ANNALS OF INTERNAL MEDICINE

PUBLISHED MONTHLY BY

The American College of Physicians

Publication Office: Prince and Lemon Sts., Lancaster, Pa.
Executive Office: 4200 Pine Street, Philadelphia, Pa.

VOL. 21 (O.S., Vol. XXVI) DECEMBER, 1944 NUMBER 6

CONTENTS

Subscription per volume or per annum, net postpaid, $7.00, United States, Canada, Mexico, Cuba, Canal Zone, Hawaii, Puerto Rico; $8.00, other countries.

Entered as Second Class Matter August 21, 1938, at the Post Office at Lancaster, Pa., under the Act of March 3, 1879. Acceptance for mailing at a special rate of postage provided for in the Act of February 28, 1925, embodied in paragraph 4, section 538, P. L. & R., authorized October 7, 1936.

. . . TO MEN OF GOOD WILL

That all men everywhere may breathe again as free men ☆ ☆ That suffering and oppression may vanish forever from the earth ☆ ☆ That all men may regain their self-respect ☆ ☆ That the labor of all men may be devoted to the good of mankind ☆ ☆ That the pain and the hurt of all men be mercifully healed ☆ ☆ That all may live in peace forever!

Wyeth

We, men and women of Wyeth . . . as one voice, make this wish. To the doctors and nurses in our Army and Navy in the far corners of the earth; to our doctors and nurses at home; to our druggists; we at Wyeth are proud to have been of service. Proud and honored to have received our third Army-Navy "E". To you, men and women of mercy—our hand and our utmost support at all times.

ANNALS OF
INTERNAL MEDICINE

VOLUME 21 DECEMBER, 1944 NUMBER 6

A HIGH FLUID INTAKE IN THE MANAGEMENT OF EDEMA, ESPECIALLY CARDIAC EDEMA. II. CLINICAL OBSERVATIONS AND DATA*

By F. R. SCHEMM, M.D., F.A.C.P., *Great Falls, Montana*

IT is only in the last 50 years that the limitation of fluids in the presence of edema has been taught and practiced so universally. Earlier clinicians noted that the theoretical fear of water in dropsy was not justified by close bedside observation.[42-45]

In 1772 Sir George Baker reported that dropsy clears in patients given large amounts of water, and comments: "I much wish to see an indulgence of this kind extended to poor thirsty dropsical patients. In making such an experiment, indulge the patient to the utmost extent. A limited permission may be pernicious."

In 1777 William Withering said: "I allow, and indeed enjoin, my patients to drink very plentifully of small liquors through the whole course of the cure," and added in 1785 after citing his 163 cases, that: "This direction is the more necessary as they are very generally prepossessed with an idea of drying up a dropsy by abstinence from liquids and fear to add to the disease by indulging their inclination to drink."

In 1786 Sir Francis Millman, "lest futile and exploded theories should be set against facts and experience," cited some 40 examples and concluded: "To irritate the body with medicines and prohibit drink is prejudicial to the patient. Treatment will be much more fortunate with large and frequent draughts of diluting drink."

In 1845 John Darwell brought such observations well into the nineteenth century: "The vulgar opinion which formerly prevailed that fluids ought not to be allowed to dropsical patients (is) completely exploded, . . . the restriction from fluids is not only not beneficial but in many cases even injurious . . . much additional evidence has been obtained to the same purpose."

* Received for publication December 23, 1943.
Read at the St. Paul meeting of the American College of Physicians April 22, 1942.
From the Medical Department of the Great Falls Clinic, Great Falls, Montana.

These voices fade as fascinating new theories [9] about edema and congestive heart failure prevail over observed facts, although for a time Austin Flint [47] and Osler [48] repeated after Dickinson that in nephritis "Of all diuretics, water is the best." In the last decade only a few clinicians [49, 50, 51, 52] have seen limited or probable indications for water in edematous patients, and ideas about edema seem little affected by Newburgh's [4] significant observation that edema in nephritis yields to an intake as high as four liters daily.

The clinical application of his renal-function and water-balance work [1, 2, 3] and its extension by Coller and Maddock [6, 7] to surgical problems were observed at first hand by the author from 1930 to 1933. It was noted that certain of their cases had grossly abnormal hearts which tolerated large amounts of water by mouth or by vein, but that, in violation of water balance principles, other cases of *primary* cardiac disease with edema were commonly subjected to a restriction of fluids or were allowed only enough water for the relief of thirst, if they were capable of complaining of it. It appeared rational to try the effect of a high fluid régime with an actual forcing of fluids on all edematous "brine-logged" patients, especially those with cardiac disease.

Method of Study

The actual clinical study was begun in 1933 in a general hospital of 200 beds, without internes or residents. *The régime*, as described in detail in Part I of this report,[67] was put in force during the periods of observation by giving:

(1) A large Amount of Water, orally or by vein (see table 7 for amounts).
(2) A "neutral" Diet to regulate the ingestion of sodium, to insure:

(*a*) Reduced Amounts of Salt and Sodium and a slight
(*b*) Excess of Acid-Ash. Small amounts of Acid Drugs were usually given to augment the effect of the diet. (See table 2 for the individual importance of the *amount of water, amount of sodium*, and the *diet reaction*.)

Other therapy was determined by the primary disease. When compatible with the safety of the patient, digitalis, mercurial diuretics, and even acid drugs were withheld until the edema cleared; thyroid extract and vitamin B were given only after edema had disappeared; acacia, hypertonic solutions and aminophyllin were not given. The diet protein was sometimes reduced from 65 to 40 grams daily until edema had cleared.

Clinical Data. (1) The *history* included the recording of immediate prior therapy, especially (*a*) the amount of rest, digitalis, oxygen, acid drugs and mercurial diuretics; (*b*) the size of the fluid intake; (*c*) the amount of salt or basic-ash foods in the diet.

(2) The *examination* for the status of the edema was usually made every morning: (*a*) puffiness, fullness, and the presence and depth of pitting over the periphery of the body from face to feet, especially posteriorly, were noted; (*b*) the level of hydrothorax and distribution and level of râles over the lung fields; (*c*) the level of the liver edge, signs of free fluid, and the degree of fullness and tension of the abdomen were recorded.

(3) *Water balance data,* incomplete but practical, were obtained by recording: (*a*) the weight, before breakfast daily whenever possible, (*b*) the intake of fluid, and (*c*) the output of urine for the 24 hours (and any abnormal losses via the gastrointestinal tract). Weight change was corrected for caloric intake, especially at the stage when edema was occult. Clinical evidence of *true* dehydration was sought for, and fever, diaphoresis, hyperventilation, and high external temperature were noted as guides to the amount of *plain* water needed. Vomiting and diarrhea were noted; and signs of excessive electrolyte loss, especially after forced mercurial diuresis, were sought as guides to *salt and water* replacement.[2, 7]

Laboratory Data. In about half the observations the following data were obtained, often every few days: the hematocrit,* the plasma or serum proteins (salting-out and falling-drop methods, usually simultaneously),† the plasma chlorides and the carbon dioxide combining power of the blood.‡ The daily albumin loss and chloride excretion in the urine,§ the maximum specific gravity of the urine,** the venous pressure in centimeters of blood, and the vital capacity, were frequently determined.

The really vital data for this study, however, were clinical and obtainable at the bedside with *a scale* and *a graduate,* and by a careful *history* and frequent *examination* of the patient.

Material

By the end of 1941, in a little over eight years, a wide variety of appropriate cases had been observed; all showed either marked gross edema or advanced cardiovascular disease. In table 1 the 402 cases and the 626 separate periods of treatment are classified according to the degree of edema present.

Table I

	With Gross Edema			No Gross Edema (Advanced Disease)	Totals on Régime
	Massive Anasarca	Marked Edema	Total Edema		
Cases	172	69	241	161	402
Periods	279	114	393	233	626
With Gross Heart Disease					
Cases	156	66	222	158	380
Periods	263	98	361	230	591

The 161 cases with "no gross edema" were studied because the degree of their cardiovascular disease and the complications present were such that one might expect a high fluid intake to produce edema or disaster.[53, 54, 55, 56] Of

* Wintrobe, Jr. Lab. and Clin. Med., 1932, xvii, 899.

† Greenberg, Jr. Biol. Chem., 1929, lxxxii, 545; and Barbour and Hamilton, Am. Jr. Physiol., 1924, lxix, 694.

‡ Osterberg and Schmidt, Jr. Lab. and Clin. Med., 1927, xiii, 172–175. Van Slyke and Cullen, Jr. Biol. Chem., 1917, xxx, 289.

§ Esbach's and the modified Volhard-Harvey methods (Kolmer and Boerner: "Approved Laboratory Technic," 1938, p. 107 and 162).

** Determined while patient was dehydrated or by concentration tests.

these cases, 59 were admitted with an acute myocardial infarction; 22 had rheumatic heart disease with marked mitral stenosis; and most had pitting edema of the ankles on admission or lost from four to 12 pounds of occult edema during treatment. Approximately 50 per cent had had massive edema shortly before admission, or developed it shortly after dismissal after they had stopped the régime (figure 5 and table 5).

Of the 241 cases with "gross edema," the 69 cases placed in the "marked edema" classification showed signs of passive congestion or free fluid in *either* the chest or the abdomen, and deep pitting peripheral edema of the legs reaching well above the ankles.

In the "massive anasarca" group there are 172 cases of what earlier writers would call dropsy or "anasarca with ascites"; all showed clear signs of *both* hydrothorax and ascites in addition to extensive pitting or brawny peripheral edema reaching above the sacrum. This degree of edema was studied in 279 periods of observation, 70 per cent of the gross edema periods and 45 per cent of the entire series.*

At the bottom of the table the cases with grossly evident cardiopathy, 90 to 95 per cent of all the material, are grouped according to their degree of edema. The material is further analyzed in the appendix.

General Observations

It soon became apparent that when sodium was properly regulated large amounts of water could be given with impunity and benefit to edematous patients and that the results with an actual forcing of fluids were better than those obtained by restricting fluids, whether the primary illness was nephritis, eclampsia, heart disease or some other disorder.†

The more severely ill patients who were sufficiently alert complained of extreme thirst, as has been noted by writers on dropsy since the sixteenth century, and showed marked clinical signs of "true" dehydration; their oliguria or anuria gave way to diuresis after their plain-water deficit was corrected, exactly as in dehydrated non-edematous patients (figure 1). Such patients sometimes showed the *loss of edema without loss of weight* [68] which is regarded as evidence of the presence of "thirsty" cells in a "brine-logged" body, and as due to a shift [10, 11] of the *water* of the edema fluid to dehydrated cells.‡

* By the end of 1943 there were 364 periods of observation on 212 cases with "massive anasarca" out of 513 periods on 314 cases with "gross edema."

† Preliminary reports were read at the regional meetings of the American College of Physicians from 1936 on. Since the report in St. Paul in April 1942, these observations have been confirmed by competent observers elsewhere.[69]

‡ Both this phenomenon and the loss of weight without diuresis, so commonly seen, indicate that the restriction of fluids does not more often lead to disastrous dehydration because the body utilizes the *water* of the edema fluid that is released when edema is clearing and its sodium salts are passing out via the kidneys.

The distinction is rarely made between "true" dehydration which is a plain-water deficit resulting in cell dehydration and increased *concentration* of extracellular fluid, and so-called dehydration which is a *salt-plus water* deficit with loss of extracellular fluid *volume*.[8, 10, 12, 14]

The clearing of edema was *facilitated* by the forcing of fluids, for it was possible to reduce greatly the frequency of the use, and the amounts of, acid and mercurial diuretics; and the loss of edema was so rapid that oppressive degrees of hydrothorax or ascites rarely required aspiration (table 5). In certain instances it was noted that the very high intake was *essential* to the clearing of resistant edema (table 2) and to the restoration to useful activity of a significant number of cases that had been disabled by anasarca on restricted fluid régimes.

So-called "water intoxication" was not encountered although syndromes answering this description were seen which were found to be due to loss of body-fluid *volume* or disturbances of electrolyte pattern, or to "true" dehydration.[18, 19, 39] The correction of these extracellular fluid defects was most surely effected by giving a *proper* amount of salt and a generous *excess* of plain water, particularly when renal function was badly impaired; indicating that almost up to the point of cessation of cell function the kidneys remain effective and precise "guardians of the internal environment" so long as enough [1, 2] water reaches them (figures 4, 5, 7).

Untoward Reactions. There were none in this series when the intake was oral, even though intakes over 15 liters in 12 hours are recorded and one patient averaged 9 liters daily for 40 days; one dutiful hysteric drank two quarts of iced water in two hours, developed dilatation of the stomach, and was relieved promptly by lavage.

A sense of fullness and oppression was complained of about 20 times in the course of more than 2,000 intravenous isotonic supplements (table 7). It appeared sometimes after only 100 to 300 c.c. of solution had been given, especially in nervous patients or in those who later showed a characteristic pyrogenic reaction. The sensation as a rule passed off uneventfully with larger volumes being tolerated well later. In one case, after 700 c.c. (with mercupurin) a major convulsion occurred, yet six hours later 1,000 c.c. without mercupurin were tolerated and the next day 1,000 c.c. twice. However, the sensation is regarded, whatever its cause, as an indication for stopping a venoclysis promptly.

Acute pulmonary edema (table 5) developed during a venoclysis in three very ill patients, one recovering while the high intake was continued. The other two, who died within an hour, had received about 500 c.c. of isotonic solution (one with mercupurin). Both had been admitted in a near-terminal state with uremia, one in coma after a meningeal hemorrhage. Pulmonary edema and convulsions are not uncommon terminations in such cases * on restricted fluid régimes and the usual supposition that the relatively small venoclyses precipitated the fatal episodes is not supported by certain observations.[15, 16, 17, 20]

Immediate Effect of the Régime on Edema. In the 393 periods of observation on cases with gross edema, the edema cleared entirely in 94 per cent, or 369 instances. In 17 of these periods, the patient was dying of some complicating condition such as subacute bacterial endocarditis, but died without recurrence of edema.

* Withering's Case VI is pertinent: "a fair case for a trial of Digitalis . . . the third day after my visit she suddenly expired. I found she had not taken any of the medicine. Had she died under its use, is it not probable that the death would have been attributed to it?" [43]

In 24 instances, or 6 per cent, the régime failed and the patient died unrelieved of edema. These were all cases of advanced disease with the uremic syndrome present in most and with the oral intake negligible because of nausea, vomiting or semistupor. In 13 of these instances edema had been cleared completely in one or more earlier periods of treatment (see J. S., figure 6).

Obviously, in many of the 369 instances in which edema cleared completely, the result could be properly attributed, in whole or in part, to changes in such factors as the amount of rest, digitalis, oxygen, or diuretic drugs. But in the 103 instances shown in table 2, or 26 per cent of the 393 periods

TABLE II

Gross Edema Resisting Usual Therapy, Cleared by Change to the Régime
103 control periods, with no other change

Cleared by Change:	In Water *and* Salt *and* Diet Reaction	41
Cleared by Change:	In Water only	22
(*after incomplete change régime*)	In Sodium only	25
	In Diet Reaction only	15
Recurrence of Edema from Opposite Changes:	In Water, Sodium *or* Diet Reaction only	26

of treatment of gross edema, no change was made that might effect the clearing of edema *except to institute the high fluid régime*. In 41 instances the edema which had resisted a restricted fluid régime cleared promptly when the neutral diet and a high fluid intake were begun.

In the other 62 instances of clearing, shown in the next three lines, the individual importance of the three factors involved in this change is emphasized, for edema did not clear until a deficiency in one of the factors was corrected. In 22 instances edema did not clear, in spite of a proper sodium level and diet reaction, until the water intake was sharply increased, particularly when the concentrating power (maximum specific gravity) of the urine was especially low. In 25 instances clearing occurred only when an unappreciated source of sodium salts was cut off. In 15 instances edema resisted an adequate water intake and a proper level of sodium until the diet reaction which had been rendered basic by extra fruit and vegetables (in obesity or diabetes) was corrected.*

The *recurrence* of edema was noted in the 26 additional instances shown in the last line as a result of a sharp decrease in water intake, or an increase in sodium ingestion, or a change to a diet yielding an excess of basic ash. In some patients massive edema returned when, led by some fad, they added to the "neutral" diet large amounts of basic ash in the form of carrot juice, orange juice or watermelon.

It was observed that marked edema cleared: (*a*) in classical myxedema with basal metabolic rates below minus 30 before thyroid extract was given,

* Schroeder's observation that an intake of about 3,000 c.c. increased edema when the maximum specific gravity of the urine was low (1.016) was made with diets so low in sodium that their *net reaction was basic*.[63]

(*b*) in cases with deficient diets from habit or chronic illness before a diet adequate in protein or vitamin B was given, and (*c*) in pernicious anemia even when complicated by spinal cord changes, before the blood or general condition had improved. In the course of acute febrile illnesses edema developed with oliguria (from the *diversion of water to edema formation* by sodium retained from excess basic ash) on the customary liquid diets of salted soups, fruit juices and milk; both were corrected by a simple change to neutral or acid-ash liquids. Similar effects were observed in correcting edema or oliguria by substituting calcium carbonate for *sodium* bicarbonate in ulcer cases,[19] acetyl salicylic acid for *sodium* salicylate in severe rheumatic fever, and vitamin concentrates for large amounts of orange and tomato juice in surgical cases.

Some patients with very mild cardiac disease but *marked* edema whose histories showed that they had been on diets high in basic ash or salted foods, cleared 15 or 20 pounds of edema without the use of digitalis or even acid drugs. Without the history, such patients might have been classified as examples of marked congestive heart failure with "cardiac edema" cleared by "spontaneous" diuresis, whereas others without clinically apparent cardiovascular or renal disease might be thought to have developed "idiopathic" edema.

In all very ill non-edematous patients, too, the régime with its regulation of sodium proved useful in the prevention and correction of dehydration and anuria. Thus a comatose patient with sulfonamide crystallization and an anuria of 42 hours' duration responded to 16 liters of water in 36 hours.

Such observations suggest that diet reaction and salt play a more important rôle than thyroid, vitamin, or protein deficiencies or than even moderate degrees of myocardial or renal insufficiency, in the development and clearing of edema; and that a proper *regulation* of sodium is quite as important as a proper water-balance to the correction and avoidance not only of edema but of dehydration and oliguria or anuria; and there are obviously other, more far-reaching, implications of these observations.*

Late Effect of the Régime on the Control of Edema. The immediate relief of edema in the hospital, even of edema that has resisted other régimes, is not as severe a test of a régime as its ability to control edema out of the hospital, while permitting greater activity, without shortening life.

Thirty-nine cases, 14 with rheumatic chronic valvular disease and 25 with degenerative heart disease, or 22 per cent of the 172 cases with massive anasarca, had been disabled by their anasarca and were unable to engage

* Implications such as that: the Starling hypothesis and the diagnostic and therapeutic significance of congestive heart failure require reëvaluation. The rôle of excess salt and basic ash in the impoverished diets of nutritional or war edema should be studied. The indications for a high protein diet require modification. Salt replacement in hot environments should go with a more adequate water replacement. Many serious phenomena associated with edema may be due to cellular dehydration. And that the use of hypertonic solutions by vein should cease.[5, 25, 40] Throughout this paper a clear distinction is attempted between the *facts* observed and what they appear *to suggest or imply* for as Beaumont says, "facts are more persuasive than argument, however ingeniously made."

in any useful activity for from one to nine years in spite of adequate treatment by the usual methods. On the high fluid régime their anasarca cleared and was so well controlled that they resumed nearly normal activity and were economically useful again for periods of from one to eight years. The gravity of their primary disease is indicated by the fact that 16 of the 39 died after from one to eight useful years, only 6 of the 16 suffering a recurrence of edema a short time before death. No greater objections to the continued use of the régime on the part of these patients were encountered than are met in any series of patients who are subjected to dietary regulation [69] (figures 3, 5, 8).

The Mortality Statistics from this series will be fully reported later but up to October 1944 they appear to support those observations that indicate that the long range results are more satisfactory than those obtained on restricted fluid régimes. Prognosis for life after the onset of congestive heart failure is notoriously poor; thus, in Dry's report [56] of a series of 150 cases treated by accepted methods with restriction of fluids, 40 were living after 5 years, a survival rate of 27 per cent. Of the cases with gross edema in this series, there are 156 cases with advanced heart disease as their *primary* disease who survived the initial admission and all but two have been traced. Of the 154 cases whose status is known, 102 were started on the high fluid régime more than five years ago and 40 of them are living after five years, a survival rate of 39 per cent. The comparison in favor of the high fluid régime seems more than fair since 74 cases, or 72 per cent of the 102 cases, showed the degree of edema described above under "massive anasarca" when they were first seen five years ago, and in 22 of the 102 cases, or 21 per cent, the onset of their congestive failure preceded their start on the high fluid régime by an average of 6.3 (2 to 15) years.

Specific Observations and Comments

The data shown are from cases with severe advanced disease, marked resistant edema, and complications that might be expected to respond disastrously to a high fluid intake. Such cases were selected for presentation because mild disease and its edema often respond to such simple measures as rest, and quite often in spite of, rather than because of, some more imposing therapy. The diagnoses and the advanced degrees of disease of the cases in the last four figures were verified at a well known medical center.

Figure 1. The Universal Response of Oliguria to Water and of All Forms of Edema to the High Fluid Régime: This figure offers a comparison of the data commonly obtained during the first few days of treatment of patients, both with and without edema, who are suffering from a lack of plain water. In the six cases there is the same early discrepancy between water intake and urine output. The first two cases were not edematous and are from Coller and Maddock's early work.[6] The next four had developed massive edema in the course of four different primary illnesses;

they were seen early in this study and received no acid or mercurial diuretics to produce a forced diuresis.

J. N., male, age 26 (Coller): A normal young adult, after four days experimental deprivation of plain water, developed oliguria, nitrogen retention, abnormal urinary findings, increased specific gravity of the blood and a loss of 6 per cent of his body weight in spite of an adequate caloric intake. The data are taken from the first days after he was permitted to drink again; in the first day he drank over 6,000 c.c.* of

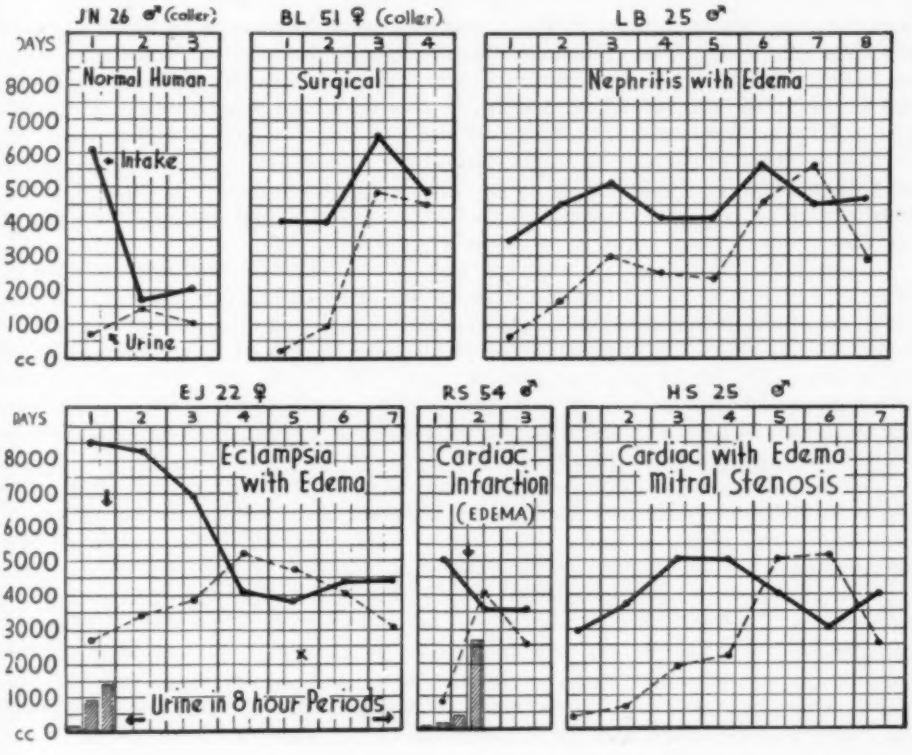


FIG. 1. The universal response of oliguria to water and of all forms of edema to the high fluid régime.

water, of which less than 600 c.c. reached the kidneys. The second day, diuresis occurred with correction of the azotemia and the 9 gram salt retention; and not until the third day was the normal relationship between intake and output, as shown in an earlier control period, reëstablished.

B. L., female, age 51 (Coller): A typical example of the correction of a water deficit anuria in a seriously ill, non-edematous surgical patient; she had lost one

* Certain obvious abbreviations are used: *c.c.* stands for cubic centimeters of water or solution; *cm.* after the venous pressure readings, stands for centimeters of blood; *mg.* is used for milligrams per 100 cubic centimeters; CO_2CP followed by the reading, stands for the carbon dioxide combining power of the blood, and volumes per cent; *grams* after serum protein, is used for grams per cent of total serum protein, and the number given in *parenthesis* is the number of grams per cent of the serum albumin fraction. The figures after *blood pressure* refer to systolic and diastolic pressures measured in millimeters of mercury.

kidney years before. Her azotemia was marked. The degree of true dehydration was such that 8,000 c.c. of water in the first 48 hours did not adequately correct the water deficit as indicated by the fact that less than 1,000 c.c. of water reached the kidney during the second day. However, on the third day, during which the intake was 6,500 c.c., the oliguria was overcome, and nearly 5,000 c.c. of urine were elaborated by the single kidney.

Case 216. L. B., clerk, age 25 in 1935, was admitted with post-infectious subacute glomerularnephritis because of swelling of the abdomen, which had increased during the preceding three weeks in spite of a low intake and purging. There was pitting edema of the abdominal wall and extremities, and edema of the face. The liver was palpable, ascites was present, and dullness and coarse râles were present at the right lung base. The albuminuria was such that the urine solidified on boiling. In 10 days on an average daily intake of over 4,500 c.c., with intravenous supplements for five days, all signs of edema and ascites cleared with a weight loss of 20 pounds and a drop in blood urea from 64 to 16 mg. During the first day there was perceptible increase in edema, yet by the end of the second day, while the urine output was still about 6,000 c.c. below the intake for the two days, there was marked clinical improvement. The only clinical residuals in 1943 are a slight cardiac enlargement and the low fixed specific gravity of the urine of 1.015.

Case 229. E. J., ranch housewife, age 22 in 1935, was admitted in coma on March 13 at 2 a.m. in the eighth month of her pregnancy. Ten major convulsions had occurred in the eighteen hours prior to admission; it was known that she had not voided for 25 hours, and catheterization yielded only 60 c.c. of urine which solidified on boiling. The blood pressure was 180 mm. Hg systolic and 100 mm. diastolic. Gross generalized edema was present; the face was blotchy and cyanotic, the breathing stertorous and the tongue badly injured. The fundi showed diffuse retinal edema with small retinal hemorrhages on the right.

Convulsions were controlled with sodium phenobarbital. Operative intervention did not appear advisable and the high fluid régime was tried on the basis that the convulsions and coma, as well as the anuria, might respond to the correction of a severe plain-water deficit and relief of cellular dehydration.*

During the first eight hours 4,000 c.c. of isotonic dextrose were given, 2,000 c.c. by vein and 2,000 c.c. subcutaneously and only 175 c.c. of urine were obtained by catheter. By 4 p.m. 14 hrs. after admission, when 6,000 c.c. had been received parenterally and only 1,000 c.c. of urine had been obtained, she roused and asked for water. In spite of a perceptible increase in edema her clinical improvement continued, no convulsions occurred, and she drank 1,000 c.c. of water by midnight with little urging. She received over 8,000 c.c. of water daily, for the first two days (the arrow indicates the time of the first definite clinical improvement, interpreted as due to the correction of her water deficit). Edema began to clear on the third day, disappeared rapidly from the fourth day on when diuresis began, and was no longer detectable by the end of the sixth day with the average daily intake at 6,000 c.c. Labor, induced on the fifth day, resulted in a stillbirth, although fetal heart sounds were present until

* During 1934 some edematous, non-pregnant patients admitted with major convulsions had responded well to the régime; epileptic convulsions seemed better controlled; convulsions in acutely ill children responded well to swift rehydration (a 22 kilogram child received a liter of isotonic dextrose by vein, aroused in three hours thirsty, and drank 3.5 liters of water in the next ten hours); and brain injury cases were managed for weeks with from 3 to 5 liters of isotonic solution daily by vein, with recovery.

Such results suggested that brain cell injury from the effects of cellular dehydration might actually be an important factor in the production of convulsions. This hypothesis, which an associate [58, 59] has described, is at least no more inadequate than the "edema of the brain" hypothesis which has led to the practice of restriction of fluids and the use of strong hypertonic solutions.

the second stage. With careful supervision on the high fluid régime she bore living children uneventfully in 1937 and 1939. In 1944 vascular injury is still occult.

A similar case, W. L., age 24, was seen recently; both mother and child survived. The intake was 5,000 c.c. the first day and 9,200 c.c. on the second day when her clinical improvement began in spite of perceptible increase in edema. The urine output the first day was 900 c.c. and diuresis and the clearing of edema did not begin until the third day; the average daily urine output continued at 7,500 c.c. for three days. On the second and fifth days there was no laboratory evidence of any disturbance in the composition, concentration, or volume of the blood.

Case 90. R. S., rancher, aged 54 in 1934, was admitted for repeated, violent Adams-Stokes convulsions which ceased when 5,000 c.c. of water had been received and less than 800 c.c. of urine had been elaborated (see figure 2 for the typical hourly urine output of such re-hydration periods). He recovered from shock and the convulsions ceased, as indicated by the arrow, before diuresis began and in spite of the same perceptible increase in his massive generalized edema noted in the case above. Edema cleared by the end of the sixth day on an average daily intake of 3,800 c.c.

Case 169. H. S., male, clerk, age 25 in 1935, was admitted with massive edema of the lower extremities, moderate bilateral hydrothorax, and ascites of two months'

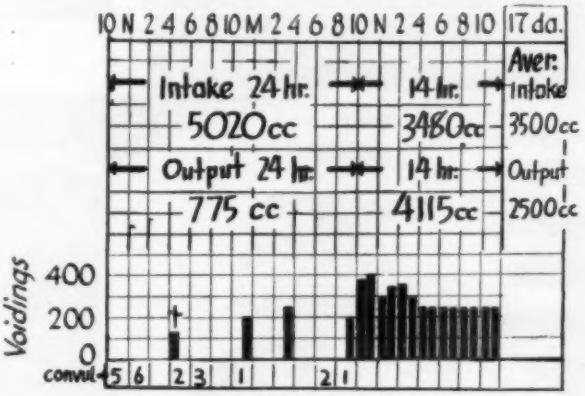


FIG. 2. R. S., No. 90. Acute myocardial infarction.

duration. There was a history of rheumatic fever, the heart was much enlarged, and mitral stenosis and auricular fibrillation were present. After 16 cat units of digitalis in the first 24 hours the apex rate dropped from 170 to 80 per minute, the pulse deficit disappeared and there was considerable symptomatic relief. In spite of these digitalis effects the oliguria persisted for two days and there was no diuresis until the fifth day, although there was continued marked general improvement. After diuresis began edema cleared completely by the seventh day with a weight loss of 17 pounds, on an average daily intake of 4,600 c.c. The blood urea dropped from 60 to 30 mg. He tolerated light work and a high fluid régime with no recurrence of edema until he died in 1937, from subacute bacterial (*Streptococcus viridans*) endocarditis.

Comment. These cases emphasize that true dehydration exists in the more seriously ill edematous patients since the correction of their oliguria follows the same pattern as in dehydrated non-edematous patients.[6, 8] The response of such patients to a high fluid intake suggests also that many of the phenomena which we attribute to edema may in fact be due to cellular

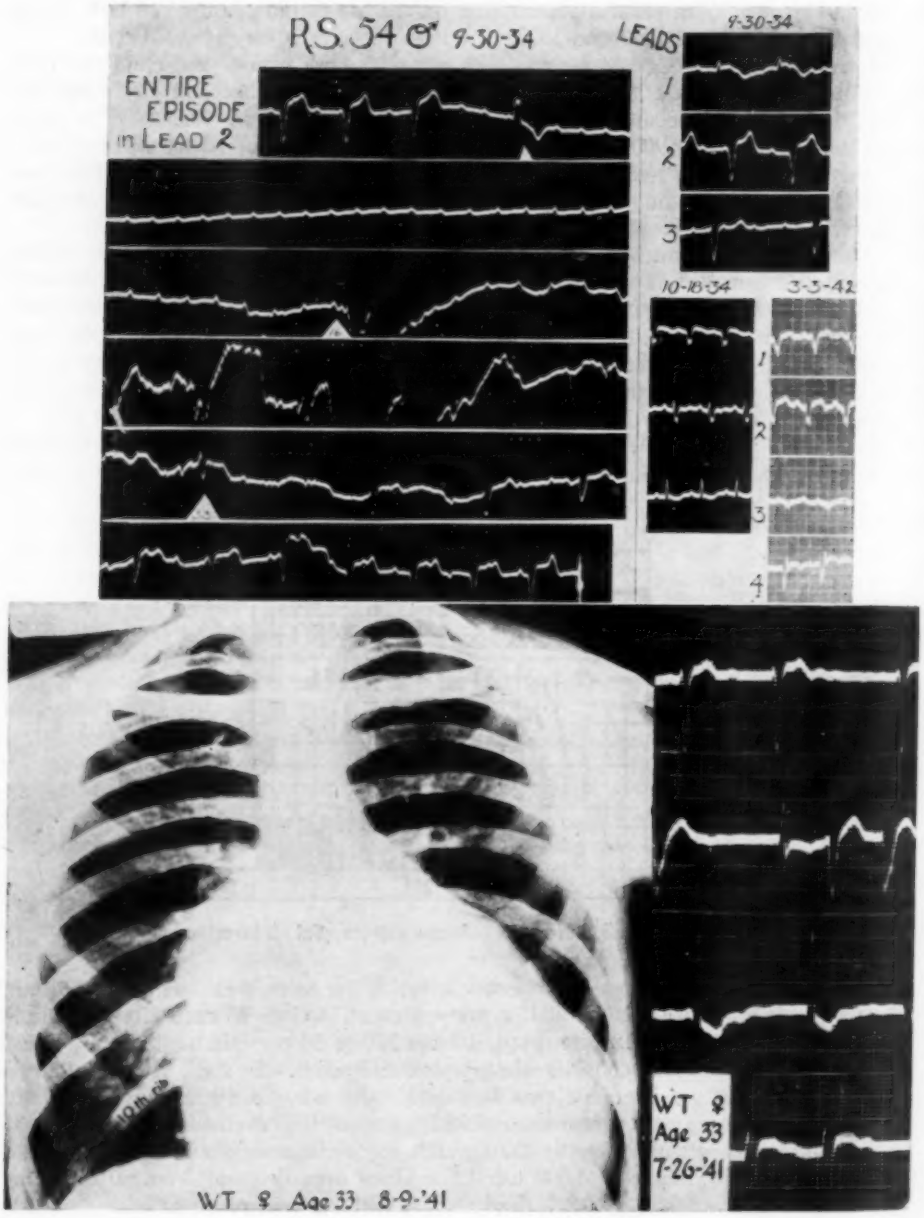


FIG. 2A (Above). The first tracing from Case 90, figure 2, covers an entire Adams-Stokes convulsion and shows, as the white wedges indicate, a duration of ventricular standstill of 33 seconds, the convulsion beginning at 16 seconds. The standard leads on that day, 9/30/34, show changes compatible with an acute myocardial infarction, and the complete A–V dissociation which disappeared within 36 hours. The tracings of 10/18/34 show an atypical right bundle branch block and other changes which persist, with slight alteration, in the 3/3/42 record seven and one-half years later.

FIG. 3A (Below). The roentgenogram of the chest and the electrocardiogram from Case 155, figure 3 are representative of many obtained from the 70 cases of rheumatic valvular disease in this series.

The 8/9/41 film was taken standing in full inspiration at 6 feet *after* the loss of 50

dehydration, for the same symptoms and signs may be relieved in the edematous and non-edematous alike by the correction of a plain-water deficit; and the clinical improvement in the edematous often precedes diuresis and is not hindered by transient increase of the generalized edema. Finally, the response of the four edematous cases to the high fluid régime indicates that the volume increase of interstitial fluid which we call edema responds to the same therapy in the same way regardless of what primary disease is present.*

Figure 2. Acute Myocardial Infarction: The high fluid intake seemed very effective in overcoming the oliguria, shock and azotemia which were encountered in about half of the 114 cases of acute myocardial infarction; 55 of these cases, like the case shown in this figure, had marked edema. In this case major convulsions from ventricular standstill, and an anuria of 20 hours' duration, were relieved. (See his figure 1 data.)

Case 90. R. S., rancher, age 54 in 1934, had had increasing shortness of breath on exertion for several years. He was admitted, six days after a typical acute coronary occlusion, in shock with a blood pressure of 90 mm. Hg systolic and 50 mm. diastolic, and with basal râles, a tender palpable liver, and generalized edema. He had not voided during the preceding 14 hours, and the 125 c.c. of urine obtained by catheter, six hours after admission solidified on boiling. Severe Adams-Stokes convulsions were occurring, four before and 11 in the first four hours after admission. The ventricular rate between standstills was about 40 per minute (figure 2A). Because he failed, in spite of oxygen and adrenalin and because of the signs of congestive failure present, he received 8 cat units of digitalis in the first six hours, in addition to two 500 c.c. intravenous supplements of dextrose after the first four hours, and all the water he could take orally between his attacks. (The black columns represent the hourly voidings in the two hour periods into which his first 38 hours are divided; the voidings of the last eight hours totaled 1,920 c.c. and are averaged at 240 c.c. per hour.)

The first specimen of 125 c.c., obtained six hours after admission, was all the urine elaborated in 20 hours; in the next seven hours only 200 c.c. were obtained, and in the last 11 hours of the first 24, only 450 c.c. The convulsions, as shown at the bottom of the figure, occurred in lessening frequency as rehydration proceeded and ceased by the end of the 24 hours when the intake had reached 5,020 c.c. and the output of urine was only 775 c.c. During this period of clinical improvement there was perceptible increase in the edema and the rate of urine excretion remained low, about 20 c.c. per hour the first half, and 40 c.c. per hour in the last half of the 24 hours, in contrast to the rate of 300 c.c. per hour during the 14 hours of diuresis that followed. About six hours after diuresis began, the complete heart block disappeared

* See also cases 226–239, tables 3 and 6. In some instances, even the ascites of carcinomatosis, and the hard, tight edema of deep femoral vein thrombosis cleared rapidly after the régime was begun; which recalls Starling's remark on experimental edema of the tongue: "One can, however, produce a very fine oedema . . . by the injection of a large amount of normal saline into the circulation." [9, 65, 66]

---

pounds of anasarca and ascites, to avoid exaggeration of heart size by any elevation of the diaphragm; a film one month later was identical.

The electrocardiogram is characteristic, with auricular fibrillation and changes compatible with marked right ventricular preponderance and/or right bundle branch block; chest lead is IV F. (See tracing in figure 5 for other characteristic changes.)

with a rise in the ventricular rate from 40 to 80 in the next four hours. With diuresis the edema cleared rapidly and convalescence was uneventful during the next 17 days while his intake averaged 3,500 c.c. daily. The blood urea dropped from 75 to 23 mg. by the fifth day. He continued moderately active through 1943 and controlled edema by periodic returns to the high fluid régime.

A similar case (92), E. P., male, age 50 in 1941, was admitted five days after a posterior infarction, in extreme shock with the blood urea at 196 mg. Anuria persisted for 42 hours until 10 liters of water had been received. Much of the average daily intake of 5,000 c.c. of water was dissipated by fever and diaphoresis and the edema and oliguria persisted until the fourteenth day, after which diuresis began and the clearing of edema and azotemia was rapid. Isotonic intravenous supplements totaling 3,000 c.c. daily were tolerated during the 14 most critical days.

Another case (89), J. A., male, age 62, with mitral stenosis and aortic regurgitation, was admitted with massive edema two weeks after a posterior infarction. The edema cleared with a 20 pound loss of weight in eight days on an average daily intake of 4,000 c.c. The clinical diagnosis was confirmed at autopsy following an acute anterior infarction a year later.*

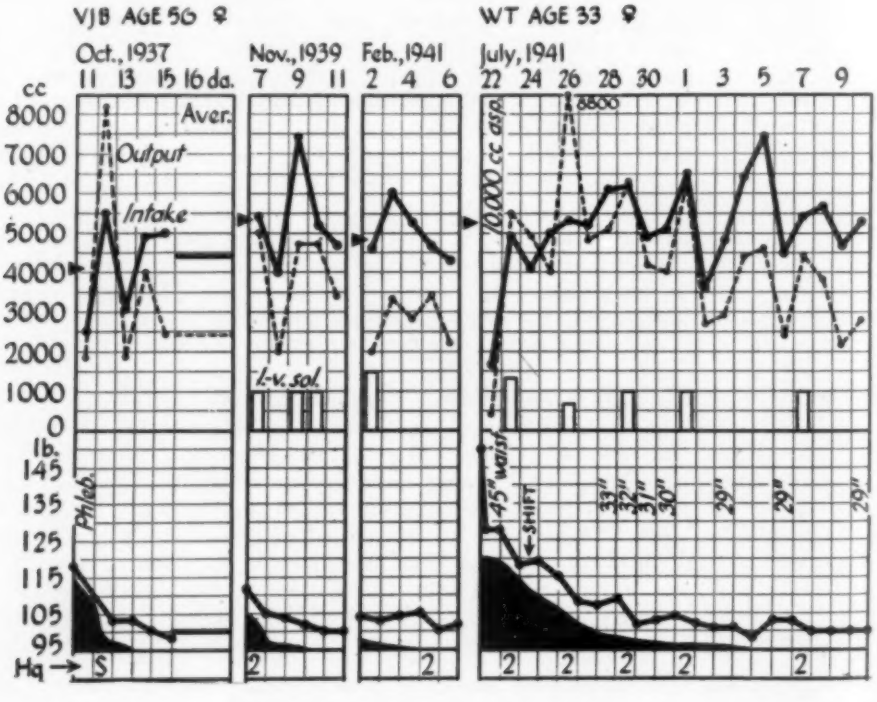


FIG. 3. Chronic valvular heart disease.

Comment. Such cases indicate that a badly and recently injured myocardium tolerates a high fluid intake well with the correction of shock, oliguria and azotemia, and with the clearing of edema when it is present.

Figure 3. Chronic Valvular Heart Disease: In the entire series there

* Courtesy Dr. J. M. Askey.

were more than 60 cases with marked narrowing of the mitral valve (25 of these with aortic insufficiency) as a result of rheumatic endocarditis, the diagnoses of which were based on the presence of characteristic diastolic murmurs. Most of the 73 instances of auricular fibrillation were found in these cases. Both of the cases in figure 3 had auricular fibrillation and aortic regurgitation in addition to mitral stenosis. The first case also had hypertension of a magnitude of 230 mm. Hg systolic and 120 mm. diastolic. The size of the fluid intakes recorded in the two cases is the more striking because their edema free body-weight was less than 100 pounds (45 kg.).

(In the upper tier of the figure, the *heavy black line* shows intake for the day; the *black wedge* indicates the average daily intake for the period; the *plain columns* represent the total volume of isotonic solution given by vein during the day; the *light broken line* shows the daily output of urine. In the lower tier the *heavy black line* represents weight and the *solid block* indicates the degree of edema present. At the bottom of the figure the use of a mercurial diuretic is indicated by the letter S for a suppository, or the number 2 for 2 c.c. of diuretic given by vein.*)

Case 159 (Left). V. J. B., housewife, age 56 in 1937. Her history included scarlet fever and three attacks of rheumatic fever between the ages of six and 14, four pregnancies carried with difficulty between the ages of 22 and 27; and hospitalization at the age of 47 with the onset of auricular fibrillation in October 1928, for her first severe break in compensation. From that time she remained economically useless because of recurrent anasarca in spite of long periods of rest in bed at home, 14 hospitalizations, and adequate and accepted treatment by a competent internist. During these nine years she was digitalized and received intravenous mercurial diuretics, acid drugs and a low salt diet, and several phlebotomies were done because of attacks of left ventricular failure. From 1934 on the blood pressure rose; in 1937 it ranged from 210 mm. Hg systolic and 100 mm. diastolic to 230 mm. systolic and 120 mm. diastolic; albuminuria was always present during her worst breaks. In the year preceding the first admission shown here, distress was continuous in spite of four hospitalizations and many weeks in bed at home.

In the *October 1937 admission,* pitting edema reached to the scapulae posteriorly, right hydrothorax and moderate ascites were present, and the liver pulsated and its edge was palpable at the level of the umbilicus in the mid-line. Extreme dyspnea, orthopnea and cyanosis were present and with the patient in a sitting position, the neck veins were much distended.

The only changes made in her previous régime were to increase her fluid intake and place her on a neutral diet. A 200 c.c. phlebotomy was done on the first day. A mercurin suppository, given on the second day, resulted in a tremendous diuresis even though mercupurin by vein had been previously ineffective. She tolerated an intake of 5,500 c.c. on the second day and a daily average of 4,200 c.c. for the five days, during which her weight dropped 20 pounds and all detectable signs of edema disappeared. There was no recurrence of edema during the next 16 days, the weight remaining at 100 pounds on an average daily intake of 4,200 c.c. The liver decreased greatly in size and orthopnea disappeared for the first time in 18 months.

* Mercurial diuretics were not observed to produce any evidence of renal injury when the water intake was adequate, even in nephritis. They were used to assist in clearing edema in only the more resistant or more distressed cases, and occasionally to test for the presence of occult edema.[61]

She followed her régime faithfully at home, taking a measured 3,000 to 4,000 c.c. of water daily. She resumed her housework and some social activities for the first time in nine years. In the past seven years she has been too active and minor lapses in the régime have resulted in the development of perceptible edema which she has controlled at home by resumption of the régime, without mercurial diuretics. She has been hospitalized only four times since 1937, for periods of from five to seven days. The *November 1939 admission* was precipitated by a digestive disturbance which put her off her régime; she cleared 10 pounds of edema in four days on an average daily intake of 5,400 c.c. with three intravenous supplements of 1,000 c.c. On the third day she tolerated 7,500 c.c. in 24 hours. The *February 1941 admission* was for an acute respiratory infection; she cleared a few pounds of occult edema on an average daily intake of approximately 5,000 c.c. There have been two other similar admissions through 1943.

Case 155 (Right). W. T., ranch housewife, age 33 in 1941 (figure 3 A), had severe rheumatic fever in March 1940 during her fifth pregnancy, which was terminated successfully in December 1940, but was followed by increasing weakness and shortness of breath. She was hospitalized from February 9 to June 15, 1941, during which time anasarca appeared and increased in spite of digitalis, the restriction of fluids, and transient response to mercurial diuretics; during a month of strict bed rest at home, prior to admission, her symptoms and the size of her abdomen increased steadily.

On *admission on July 22, 1941,* at noon, extreme orthopnea, dyspnea and intense cyanosis were present. The signs of hydrothorax extended to the mid-scapula on the right and covered the lower one-third of the lung field on the left. The abdomen was greatly distended and the enlarged liver was ballottable through the ascitic fluid. Pitting edema extended to the mid-scapulae and was present over the lateral abdominal walls, and the edema of the thighs and legs was tight and brawny. Ten liters of ascitic fluid were permitted to flow through a small trocar over a period of 90 minutes with the resultant loss of 22 pounds of weight, but with only moderate relief of her extreme dyspnea and orthopnea and much ascitic fluid remained after the aspiration. The neck veins remained distended when the patient was sitting, and the venous pressure, four hours *after* aspiration, was 23 cm. of blood (25 cm. with liver pressure). There was no spontaneous diuresis following the aspiration. She was permitted to rest the balance of that day.

The régime was started the second day. There had been no change in the peripheral edema or the level of hydrothorax overnight, and she still complained of intense thirst, as she had on admission. On this first day of the régime, with the venous pressure unchanged, she tolerated 1,300 c.c. by vein with a total intake of 5,000 c.c. and lost 10 pounds of weight. In the next 24 hours there was no further weight loss, although there continued to be a further marked loss in edema, indicating a shift of water to the cells during that time. By the fourth day the venous pressure had dropped to 7.5 cm. of blood. By the end of the twelfth day of the régime, on an average intake of 5,500 c.c. daily, she had lost all evidence of peripheral edema, ascites, and hydrothorax with a loss of 28 pounds of weight (in addition to the 22 pounds removed mechanically on the day of admission).

At the level of the umbilicus the abdomen measured 45 inches on admission, 30 inches on the eighth day, and 29 inches at the time of discharge, although the actual caloric intake during her last 10 days exceeded 3,000 calories daily. After dismissal she gained 18 pounds of true body weight by October 10, on which date the circumference of the abdomen was only 28½ inches.

This 45 kilogram (100 lb.) woman (whose total blood volume was about 4,000 c.c. and whose normal interstitial fluid volume [12] was about 7,000 c.c.) was relieved of about 23 kilograms of excess extracellular fluid, while the average daily water intake

was 5,500 c.c., with a maximum in one day of 7,500 c.c., and while there was an average daily output of urine water, in the first five days, of 5,600 c.c., with a maximum on the fourth day of 8,800 c.c. Yet, from the first to the sixth day, the plasma chlorides rose from 511 to 594 mg. and the CO_2CP changed only from 66 to 67; and in another 12 days with the average daily urine output at 4,300 c.c. the chlorides dropped only to 577 mg. and the CO_2CP to 61. On the same days (2nd, 6th, and 18th) with the diet protein at 70 grams, the serum proteins were 6.0 (3.2), 5.4 (3.0) and 5.2 (2.9) grams and the hematocrit readings were 44, 53, and 51 per cent.

General improvement continued during August, with bed rest at home. The régime was well followed and there was no recurrence of edema. By October she had resumed full care of her ranch home and five children. On October 10 and December 12, 1941, after a 200 mile drive from her home she showed no evidence of even peripheral edema; she was taking a *measured* 4 liters of water daily. She continued active and edema free until her sudden (embolic) death in February 1942.

A similar case (156), B.P., male, age 28 in 1939, whose roentgenograms and electrocardiograms were like those of W. T's, died in uremia in March 1942. Autopsy showed multiple, large, fresh pulmonary infarctions and a mitral orifice narrowed to a slit that just admitted loosely the handle of a scalpel. In May 1941 he tolerated for 21 days an average daily intake of 6,000 c.c., including 2,000 to 3,000 c.c. by vein daily the first eight days, and cleared his edema completely with a weight loss of 25 pounds.

Comment. Such cases as these show that hearts handicapped by obstructed and incompetent valves and auricular fibrillation tolerate the high fluid régime even in the face of high venous pressures,[34] arterial hypertension, and myocardial damage. In cases like V. J. B. the difference between the nine years of disability and the seven years of useful activity appears to lie in the difference between the restricted fluid régime and the high fluid régime (see also A. V. F., figure 5). The cardiac veterans who have followed both régimes faithfully, have generally found the high fluid régime the lesser of two evils and more effective in controlling their edema.

The data from W. T. indicate also how well the handicapped kidneys [30, 31, 64] of severe congestive heart failure regulate the concentration and electrolyte pattern of the extracellular fluid while permitting great losses of excess interstitial fluid, in spite of the daily ingestion of volumes of water and the daily loss of volumes of urine water that actually exceed the blood volume and approach the normal volume of the interstitial fluid. There was no evidence here of the production of so-called "water intoxication" or of the "washing out" of *needed* sodium or chloride.

Figure 4. Resistant Massive Anasarca in Advanced Cardiovascular Disease: Withering comments: "If the belly be tense, hard . . . or the limbs in anasarca solid and resisting, we have but little to hope." Both the cases in this figure had massive anasarca of many months' duration, neglected or resistant, with the tight, hard swelling of brawny edema reaching well up the trunk, bilateral hydrothorax reaching to the mid-scapulae, and ascites with tight swelling of the abdomen and brawny edema of the abdominal wall. Both cases showed a high grade of arteriosclerosis and hypertension, and the second case, for good measure, had mitral stenosis and myelogenous leu-

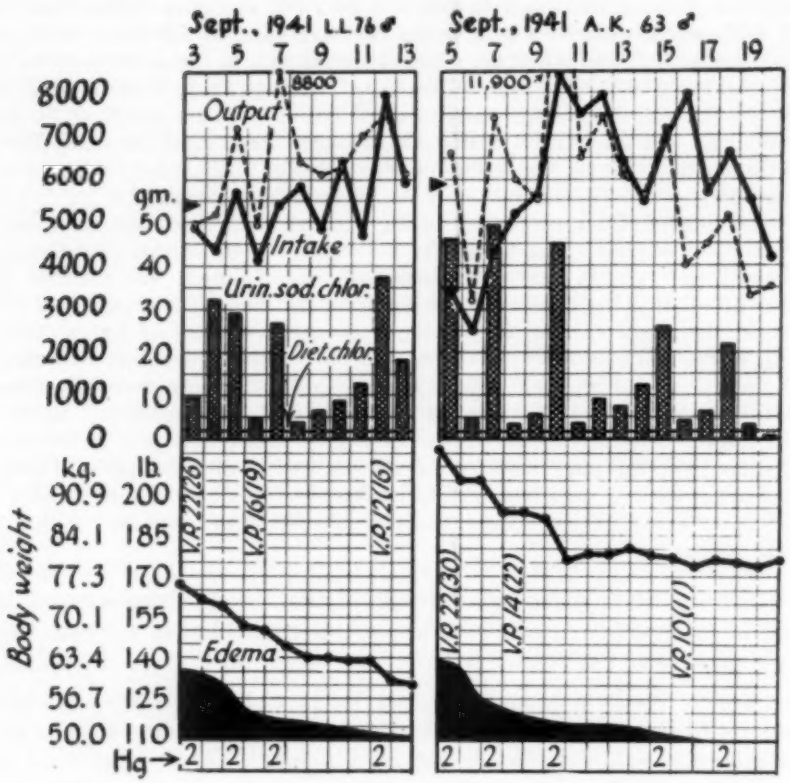


FIG. 4. Resistant massive anasarca in advanced cardiovascular disease.

kemia. The first patient complained bitterly of thirst on admission and both patients showed a maximum specific gravity of the urine of 1.016 or less.

Case 1 (left). L. L., male, retired, age 76 in 1941, had had cardiac symptoms for 14 years; a blood pressure of 200 mm. Hg systolic and 120 mm. diastolic in 1927; angina of effort since July 1931; increasing dyspnea and edema since 1937; and there had been massive swelling of the legs and abdomen for four months prior to admission. The examination showed the extent and kind of anasarca, with ascites and hydrothorax, described above.

His thirst was still intense after 2,000 c.c. of water (as isotonic dextrose) by vein and 1,500 c.c. of water taken eagerly by mouth. He lost 37 pounds of edema in 10 days with an average daily intake of 5,500 c.c. Most of the edema cleared in the first six days, but there was a perceptible loss of edema in the next three days without further loss of weight,[68] indicating the shift of water to thirsty cells (which had been kept dehydrated by the forced mercurial diuresis). On the tenth day an intake of 8,500 c.c. did not prevent a weight loss of nearly 10 pounds. In his first 12 hours he tolerated 1,000 c.c. of isotonic dextrose by vein while the venous pressure was 22 cm. (26 cm. with liver pressure), and the pressure fell in the usual manner as the edema cleared,[70] to 16 cm. in three days and to 10.5 cm. on the tenth day.

The urinary sodium chloride excretion for 24 hours, in grams, derived in the usual manner from the actual urine chloride, is shown in the cross-hatched columns.

(Ingested chloride daily was derived from 4 grams of ammonium chloride and about 2 grams of diet sodium chloride.) There is no real parallel between the amount of urine chloride and the volume of urine water, even when a mercurial diuretic forced the kidneys, for, expressed as sodium chloride, on the second day 35 grams appear in 5.0 liters, but on the fifth day, 27 grams appear in 8.8 liters, or only half as much salt per liter of water, and on the fourth and sixth days less than 5 grams appear in 5.0 and 6.5 liters. The kidneys apparently permitted the passage of sodium and chloride or water in proportions that protected the concentration and electrolyte pattern of the internal environment; thus, in 11 days the plasma chlorides ranged from 544 to 552 mg., the CO_2CP from 62 to 54, and the plasma proteins changed from 6.1 (3.9) to 4.9 (2.9) grams in a direction opposite to the hematocrit which rose from 36 to 45 per cent. He resumed moderate activity by the middle of October, and on the régime there was no recurrence of edema throughout November and December. He died in January with uremia following an acute myocardial infarction.

Case 157 (right). A. K., male, rancher, age 63 in 1941, had had dyspnea on exertion since rheumatic fever at age 24. He had been digitalized and intermittently disabled because of edema and orthopnea since 1936, and during the year before admission there was increasing resistant anasarca and the appearance of large cervical lymph nodes. Examination: The cervical and axillary lymph nodes were enlarged and the blood smears were diagnostic of chronic myelogenous leukemia. The spleen and liver were greatly enlarged, as was the heart, which showed the presystolic murmur of mitral stenosis. The maximum specific gravity of the urine was 1.016, and the blood pressure was 170 mm. Hg systolic and 110 mm. diastolic. His degree of anasarca was that described above. He lost 40 pounds of weight in six days on an average daily intake of 6,000 c.c. The maximum intake of 8,500 c.c. was in the 24 hour period in which the output was 12,000 c.c. and the weight loss 15 pounds.* He tolerated 1,000 c.c. of isotonic dextrose by vein while the venous pressure was 22 cm. (30 cm. with liver pressure), the venous pressure dropping as indicated.

The most marked diminution in edema occurred during the second day when there was no weight loss, indicating a marked "shift" of water to the cells; a lesser "shift" is indicated after the first six days by the disappearance of the remaining detectable edema without weight loss. The last two doses of mercupurin shown were given as tests for occult edema.[61] (If there is no weight loss or if the weight loss is promptly regained it is good evidence that occult edema no longer exists; here it confirmed the impression that the residual splenomegaly and hepatomegaly were due to the leukemia.)

Here again is seen the preservative suppression of urine chloride excretion which followed mercury-induced outpourings, and the ability of the kidneys to eliminate *unneeded* plain water without *needed* salts. Thus, on the first day 46 grams of sodium chloride are recorded in 6.6 liters and on the sixth day 45 grams in 11.9 liters of water, and on the seventh day less than 4 grams appear in 6.5 liters of urine water, in spite of the daily ingestion of about 6 grams of chloride salts. Nor does a *high intake* of plain water overwhelm this selective function of the kidneys and "wash out" needed electrolyte, for on the seventh day with an intake of 7.5 liters and on the twelfth day with an intake of 8.0 liters the urinary sodium chloride remains less than 5 grams. In the 16 days of the period the plasma chlorides changed from 594

* The crude water balance figures for the 16 days here are representative: the total intake of water as such was 93.0 liters and the total urine water output was 93.9 liters, indicating that all of the 40 pounds of the edema fluid water, 18 liters, plus about 13 liters of the water of the solid food in the diet, or a total of about 30 liters of water, must have left the body as water of vaporization (except for about 3 liters eliminated via the stool), implying a quite reasonable water vapor loss of about 1,700 c.c. daily.

to 648 mg., the CO_2CP from 59 to 71, the serum proteins from 5.7 (3.7) to 6.2 (4.0) grams and the hematocrit from 36 to 52 per cent.

In November there still had been no recurrence of edema in spite of too great activity. By February edema had begun to recur after a five weeks' lapse from the régime, and it was imperfectly controlled at his ranch home until death, in September 1942, from leukemia.

Comment. Here longstanding brawny anasarca and tight ascites, which are hard to relieve, were cleared in spite of age, advanced hypertensive and arteriosclerotic changes, poor renal function and other complications; and both cases tolerated 1,000 c.c. of isotonic dextrose by vein, at a time when the venous pressures were above 20 cm. of blood.[34, 35] The impaired kidneys of these cases appeared capable of protecting the concentration and the electrolyte pattern of the extracellular fluid in spite of forced diuresis from mercurial diuretics.[1, 18, 21]

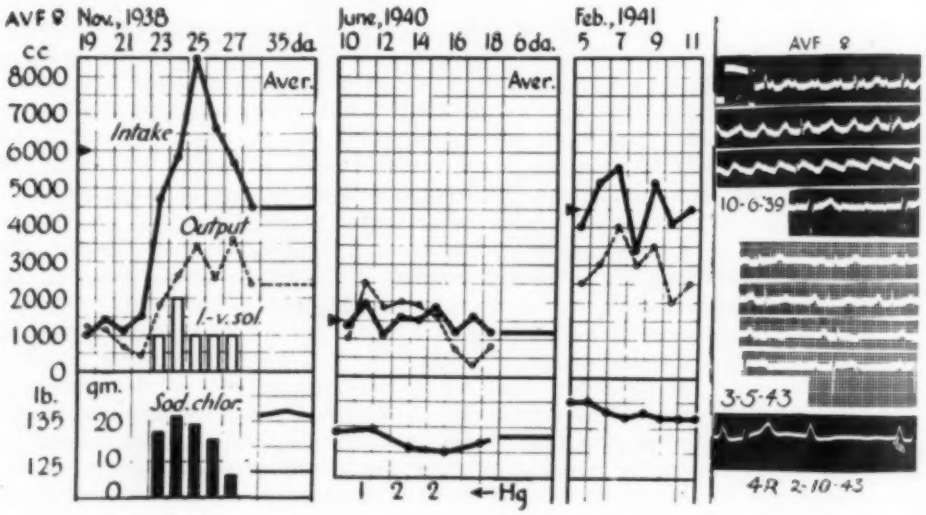


FIG. 5. Salt replacement with a high water intake in advanced heart disease.

Figure 5. Salt Replacement with a High Water Intake in Advanced Heart Disease:* This patient was a veteran of 12 years of recurrent congestive heart failure prior to 1938, when she was admitted in a critical state from a *chloride deficit* and a loss of body fluid volume. She was given 80 grams of salt with 30 liters of water in five days and tolerated an average daily intake of 4,500 c.c. for 36 more days without the production of edema. At the time of the three admissions shown here no gross peripheral edema was present, but there were such signs of passive congestion of the lungs

* The two periods of treatment on a high fluid intake shown here (and the 1940 period for V. J. B. shown in figure 3) serve as examples for about half of the 233 periods from the 161 cases with No Gross Edema in which no edema was produced during treatment on the high fluid régime, in spite of the prior existence of gross edema or its subsequent appearance when off the régime (table 1).

and liver that it was thought proper elsewhere, as is shown in the *June 1940 admission*, to place her on a restriction of fluids and use a mercurial diuretic in accordance with accepted practice.*

Case 158. A. V. F., ranch housewife, age 43 in 1938, had rheumatic fever in 1922, her first congestive failure with hemoptyses and marked edema of the ankles in 1926, and arrhythmia and syncopal attacks from 1931 on. In 1926, 1940, and 1943 she was seen at the Mayo Clinic, where the mitral stenosis and aortic stenosis, moderate congestive failure and "serious organic heart disease with marked cardiac crippling" were noted.

The electrocardiogram of October 6, 1939, in the figure is characteristic of many taken from 1938 through 1943, showing an auricular flutter (rate 240 per minute) and a slow irregular ventricular beat, the rate varying from 35 to 70 per minute, quite unaffected by digitalis. In the three standard leads the QRS complexes do not exceed 5 millivolts in height and the flutter waves are large and notched. The March 5, 1943 tracing shows a transient period of normal rhythm and a P–R interval of 0.24 second without digitalis. On February 10, 1943, during a syncope at the Mayo Clinic, Wenckebach periods were caught in their lead 4R, the P–R intervals varying from 0.32 to 0.40 second.

She was first seen here on November 23, 1938, when salt replacement therapy was required, as shown in the first column of this figure and as described below. The data from *the June 1940 admission* are shown in the center column to contrast the high intake of this régime with the low intake of the accepted régimes, which included also potassium nitrate, the restriction of salt, and a course of mercurial diuretics. For a year and a half prior to the June admission there, she had controlled edema and been active on the high fluid régime with a measured intake of 3,000 to 5,000 c.c. daily. But in July 1940, while on the restricted fluid régime at home, she developed marked edema with a gain of nine pounds in two weeks, which she cleared at home by voluntarily returning to the high fluid régime. The *February 1941 admission* (right hand column), for mild respiratory infection, shows that she continued to tolerate without the production of edema an average daily intake of 4,500 c.c. with no mercurial diuretics and only 2 grams of ammonium chloride daily. (In the winter of 1943 she was again advised, on the basis of accepted practice, to restrict fluids, but she continued with the high fluid régime because, she said, "I feel better and can keep the swelling down easier." That fall she cleared at home the massive edema of the legs, that developed while riding a combine during the 1943 harvest, by attention to her régime.)

The *November 19, 1938 admission:* During the preceding six months massive edema had occasioned hospitalization with accepted methods of treatment for three weeks in June, and for five weeks ending November 5. Only two days before admission on November 19, her legs had been badly swollen but the edema had disappeared coincident with frequent emeses during the 12 hours before admission. During the first four days in the hospital her condition was regarded as terminal; there was an occasional small emesis, she became too weak to move in bed without help, and the heart sounds were so feeble that the characteristic murmurs of mitral stenosis, aortic stenosis, and aortic regurgitation, which became apparent later, were not heard. The average intake of these first four days was 1,200 c.c. daily.

When she was seen on November 23, neither the history nor the electrocardiogram (identical with tracing of October 6, 1939) suggested digitalis intoxication. The

* The clinical data in the periods of treatment with restriction of fluids, shown in figures 5, 6, 7 and 8, were made available through the courtesy of Drs. A. M. Snell, A. R. Barnes, T. J. Dry, H. L. Smith, R. L. Parker and M. N. Keith; and the microscopic findings of autopsy material from the cases in figures 7 and 8 were confirmed by Dr. J. W. Kernohan.

blood urea was 54 mg. and the maximum specific gravity of the urine 1.015. The clinical impression of hypochloremia was confirmed by a plasma chloride reading of 320 mg.

Because of the edema present only two days before admission, she was placed on a liquid neutral diet so that the ingestion of salt could be better gauged. It was estimated that she would require about 76 grams of salt. By the end of 48 hours, after 40 grams of salt had been taken with 10.5 liters of water, she showed improvement in general strength and in the quality of the heart sounds. By the end of the fifth day of replacement she had received 80 grams of salt with 30 liters of water, the plasma chlorides had risen to 500 mg., and she sat up in bed and wrote a letter. There was steady improvement during these five days and no detectable evidence of the development of edema, in spite of the ingestion, on the third day alone, of 20 grams of salt and 8.5 liters of water. During the following 36 days she improved steadily while tolerating an average intake of 4,500 c.c. daily; the weight changed only from 137 to 136 pounds and no edema developed.

The 30 liters of water with 80 grams of salt received in the first five days were the equivalent of 9 liters of normal saline and 21 liters of plain water and this ratio of 1 to 2.3 permitted the correction of the chloride deficit, the total body-fluid deficit and any plain-water deficit present, without the production of edema. The urine output which had fallen to less than 500 c.c. in 24 hours before the high intake was begun, averaged 3,000 c.c. daily the last four days of the replacement period. The extra plain water here did not "wash out" *needed* sodium or chloride but only assisted the kidneys in regulating the electrolyte pattern accurately and in bringing the extracellular fluid just up to its normal volume.

Case 289. M. N., female, age 59 in 1941, presented a similar replacement problem with a *sodium deficit.* She received in the first six days 160 grams of salt (and a few grams of sodium bicarbonate) with 35 liters of water including 5 liters by vein the first day and 3 to 4 liters by vein daily for the next five days. Thus she was given the equivalent of 18 liters of normal saline solution and 17 liters of plain water. She recovered and no edema was produced, Adams-Stokes attacks ceased and the carbon dioxide combining power rose from 28 to 60 volumes per cent, while the plasma chlorides remained unaltered at 500 mg.

Comment. Such cases show that, when sodium ingestion is properly regulated, a very high intake of water, with salt as *needed,* does not produce edema even in patients with advanced disease who have had marked edema before.

It appeared that the excess intake of water, with relatively little salt, merely helped the kidneys to correct existing chloride or sodium deficits.[1, 3, 7] It was also noted that when the kidneys could no longer correct such deficits on this high fluid régime they could not correct them with an excess of salt or with the restriction of fluids, and that these latter measures only produced edema or dehydration (figure 7). Finally, it was observed that when such deficits existed in edematous patients and their edema began to clear, the kidneys often kept back enough of either sodium or chloride from the sodium chloride of the edema fluid to correct the existing deficit (figure 4). In replacement therapy here, therefore, no extra salt is given in the presence of marked edema unless the electrolyte pattern is profoundly disturbed; and,

in all situations where salt is badly needed, more plain water is given in proportion to salt than is present in a normal saline solution.*

Figure 6. Failure of the High Fluid Régime to Clear Edema: Eventually cases of advancing degenerative disease will reach a stage where they will not clear edema on any régime, although fortunately most of them die

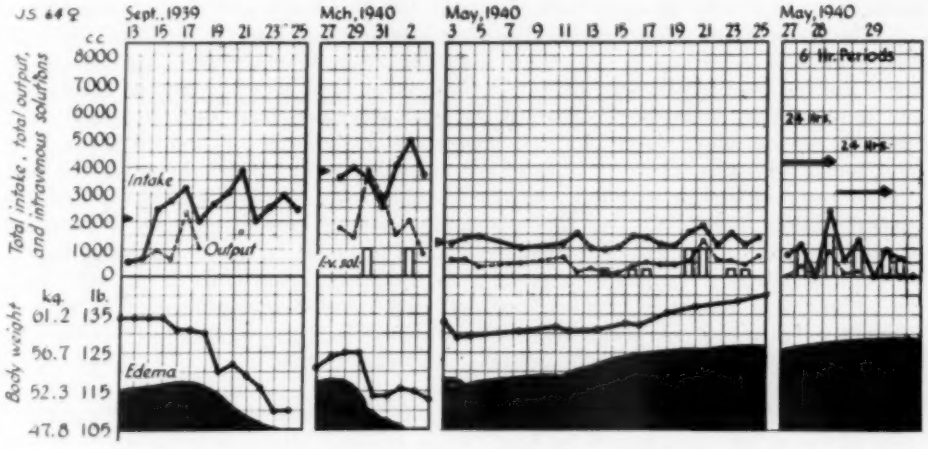


FIG. 6. Failure of the high fluid régime to clear edema.

edema free before this stage is reached. This case illustrates the futility of therapy in such cases on any régime.

Case 91. J. S., housewife, age 64 in 1939. In 1926 the blood pressure was 180 mm. Hg systolic and 140 mm. diastolic, and in 1929 the occurrence of an acute myocardial infarction was confirmed by an electrocardiogram. In 1934, after another severe infarction, she developed diabetes mellitus which she neglected, and she showed a constant moderate albuminuria. She was hospitalized three times in 1939 for attacks of coronary occlusion and left ventricular failure and responded well to the high fluid régime with, for example, an average daily intake of 5,000 c.c. for 24 days in June. She did not follow her diet in the intervals and coöperated poorly in the hospital.

The *September 1939 admission:* For the first three days while she was on a low-salt diabetic diet yielding an excess of *basic* ash her weight remained stationary and edema increased until a right hydrothorax became evident. In the next four days, after the change to the neutral diet with its excess of *acid* ash, the edema began to yield reluctantly and she lost 15 pounds. In the next five days, after two grams daily of ammonium chloride were begun, there was a further weight loss of 10 pounds with complete clearing of the edema and hydrothorax. No mercurial diuretic was used.

In the *March-April 1940 admission,* here, she still tolerated a high fluid régime with benefit, for she cleared her edema with a 12 pound weight loss in four days on an average intake of 4,000 c.c. daily.

* For therapy by vein, the minimum proportion is thought to be one part of plain water as isotonic dextrose to one part of normal saline solution, and the optimum proportion is thought to approach two or even three parts of plain water to one part of normal saline.

In the *May 1940 admission,* however, a month later, at the Mayo Clinic, with her advancing disease nearing its terminal stage, she failed to respond to 23 days of restricted fluids and other accepted measures. She received no extra salt in the little food she took, potassium nitrate was given as tolerated, and the average intake was 1,200 c.c. daily. The edema increased steadily, the blood urea rose from 40 to 110 mg., and there was some loss of vision with the appearance of fresh retinal hemorrhages. During the last 12 days her weight increased 10 pounds in spite of seven intravenous injections of hypertonic dextrose (20 per cent), and one of salyrgan.

Thirty-six hours after leaving there an attempt was made to enforce the high fluid régime here, as shown in the last *May admission* column: (the data for the 60 hours are recorded in six-hour periods). The blood urea was 120 mg. on admission, and mild uremic convulsions occurred at intervals throughout the 60 hours. The clinically severe dehydration was not perceptibly relieved in the first 24 hours by a total intake of about 4,000 c.c., the edema increased a little, and there was no real clinical response except that she roused enough to take a little liquid orally and one neutral feeding. At 2:30 a.m. in the seventh six-hour period, an acute myocardial infarction occurred, following which the signs of anoxemia were unrelieved by the oxygen. In the next 12 hours catheterization yielded only 40 c.c. of urine; yet during the 12 hours she tolerated 1,000 c.c. and 500 c.c. of isotonic solution by vein without incident. Death occurred seven hours after the last 500 c.c. venoclysis, in the midst of a mild convulsion, with a swiftly terminal pulmonary edema.

Comment. This patient as she neared the end of her illness, after several years of response to a high fluid régime, did not respond to a restricted fluid régime or to the final attempt to enforce the high fluid régime. This period shown is similar to many that make up the 24 instances in this series of complete failure of the high fluid régime to clear edema or relieve symptoms.

Figure 7. Chronic Glomerular Nephritis with the Nephrosis Syndrome and Cardiopathy: This case fulfilled the usual clinical criteria for nephrosis. The patient was followed from the insidious appearance of massive edema to autopsy; for two years his edema and the degenerative vascular complications were treated on the high fluid régime.

Case 203. F. O. G., male, was a long-distance truck driver, age 35 in 1940. His father died at age 65 of "dropsy" and his mother at age 56 of "heart failure." He had had frequent sore throats in childhood, and influenza in 1918. He was underweight but there was no detectable evidence of disease in November 1937 on examination at a medical center where his blood pressure was 100 mm. Hg systolic and 50 mm. diastolic, and his urine showed no albumin and a specific gravity of 1.026.

He was seen here, in May 1940, as an out-patient, because of swelling of the legs of two weeks' duration which followed an acute respiratory infection. The diagnosis of the referring physician, glomerular nephritis, was confirmed; a large amount of albumin and many casts were present in the urine, the fasting blood-urea was 67 mg., enlargement of the heart was noted, and the maximum specific gravity of the urine (corrected for albumin) was 1.010.

Six weeks later, as shown in the *June 1940 admission* at the Mayo Clinic, he was treated as a case of nephrosis. The edema had increased, the blood pressure range was 140 mm. Hg systolic and 90 mm. diastolic to 190 mm. systolic and 110 mm. diastolic, the blood urea ranged from 42 to 52 mg., the serum sulphate was 6 mg., the urea clearance was 30 c.c. The plasma proteins were 3.8 (2.2) grams on

the first day and 3.5 (2.2) grams on the last day of treatment in spite of a diet protein of from 100 to 120 grams. The fluid intake averaged 1,400 c.c. daily, the diet had no added salt and either 18 grams of potassium nitrate or 9 grams of potassium chloride were given daily. Because of very slight decrease in edema and a weight loss of only two and one-quarter pounds in the first five days, 500 c.c. of a 6 per cent solution of acacia were given on the sixth and eighth days, which was followed by an additional weight loss of 10½ pounds and the disappearance of edema by the twelfth day.

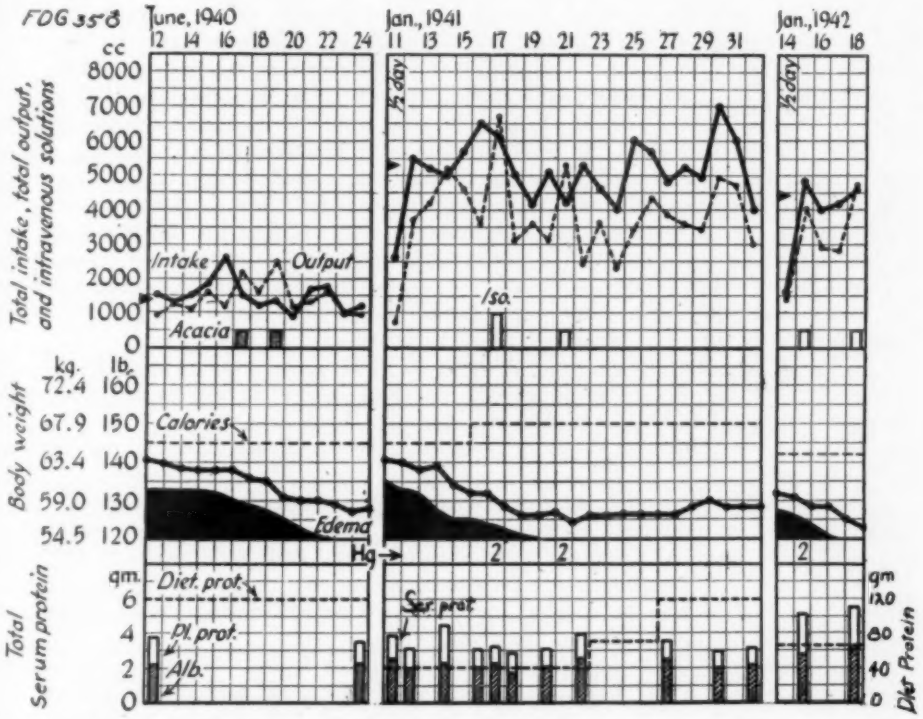


FIG. 7. Chronic glomerular nephritis with the nephrosis syndrome and cardiopathy.

He returned to his work as a trucker, the evening edema of his legs returning in a few weeks. A month before the next admission, swelling of the abdomen and dyspnea forced him to stop work; but his edema increased in spite of rest, although he followed his restricted fluid régime as faithfully as he later followed the high fluid régime.

In the *January 1941 admission* here, after six months on a régime which had restricted water to five glasses a day, he showed marked peripheral edema, with pitting to the sacral region, marked ascites and moderate bilateral hydrothorax. The heart was larger than in May 1940, and the retinal vessels were narrow and tortuous although no retinal hemorrhages were present.

During the 22 days here, the average daily intake was 5,200 c.c., the maximum in one day 7,000 c.c. Instead of 6 grams of potassium nitrate daily and the low-salt, high-protein diet, he received 4 grams of ammonium chloride and 2 c.c. of diluted hydrochloric acid daily, and a neutral diet with 2,500 to 3,000 calories, which yielded only 40 grams of protein daily (as a control observation).

On this régime all the edema cleared in nine days with a weight loss of 15 pounds on an average daily intake of 5,700 c.c. Almost all of the detectable edema disappeared with a nine pound weight loss in the six days before the first test dose of mercupurin, which resulted in six pounds further weight loss, chiefly of occult edema. During the first two and one-half days there was marked decrease in edema with a weight loss of only one and one-half pounds, indicating a shift of water to thirsty cells.

The serum proteins were frequently determined and are shown as columns in the lower tier, the hatched portions representing the serum albumin fractions.* Note that in spite of the daily loss of from 4 to 20 grams of albumin in the urine, neither the total serum protein nor the albumin fraction changed significantly in the 22 days, whether a high or a low protein diet was given. The serum protein was only 3.9 (2.5) grams on the day of admission, after the six months on a diet protein of 120 grams. After 12 days on a diet protein of 40 grams the serum protein was actually higher, 4.0 (2.6) grams; and after the next 10 days on a maintenance (65 grams) and a high protein diet (120 grams) the serum protein was actually lower, 3.2 (2.2) grams. The albumin fraction of the serum protein ranged from a low of 1.7 grams on the eighth day, by which time the edema had cleared, to a maximum of 2.6 grams on the twelfth day of the low protein diet. Note that the maximum clearing of edema with a weight loss of seven pounds, without the use of a mercurial diuretic, occurred during the fourth and fifth days, while the total serum proteins were falling from their transient high of 4.5 (2.3) grams to 3.1 (2.1) grams.

In the 22 days the hematocrit rose from 35 to 41 on the twelfth day and was 32 per cent on the last day, and the plasma chlorides rose from 540 to 640 mg. The cholesterol dropped from 480 to 232 mg., and the blood urea ranged from 50 to 55 mg. with the diet protein at 40 grams, and from 70 to 75 mg. after the diet protein was increased.

He was able to continue, against advice, his usual heavy work throughout 1941, chiefly because of intelligent management of his diet and régime, which included a measured three quarts of water daily that ensured a total daily fluid intake of 4,000 c.c.

After this year, characteristic vascular complications of his steadily progressing disease brought him into the hospital for four short periods during 1942. Some data from these and his last admission are given below.

The *January 1942 admission* only is shown in this figure. His vision had failed after two weeks of a low fluid intake because of severe headaches with nausea and vomiting. In spite of the presence of an advanced "albuminuric retinitis" with choking of the discs, and paroxysmal dyspnea and basal râles, he tolerated without disaster and with marked clinical improvement an average intake of 4,500 c.c. for five days with the clearing chiefly of occult edema with a weight loss of nine pounds. After a year with a diet protein of 65 grams the serum protein was 5.1 (2.7) grams, and rose to 5.6 (3.1) grams. The hematocrit rose from 34 to 41 per cent, the cholesterol fell from 400 to 294 mg., and the plasma chlorides rose from 632 to 700 mg.

After a similar episode in May 1942 the fundi again showed fresh hemorrhages and choking of the discs. The average daily intake for the eight days was brought to 5,400 c.c. by intravenous supplements of isotonic dextrose of 1,000 c.c. each, given twice daily for six days, without disaster and with clinical improvement. A venous pressure of 14 cm. dropped to 5 cm. by the seventh day. With the diet protein at 40 grams the serum protein rose from 4.2 (2.1) to 4.6 (3.0) grams. There were only trifling changes in the hematocrit, CO_2CP and chlorides. The blood urea ranged now from 105 to 110 mg.

In August, after a low intake due to nausea and vomiting, he was admitted with extreme orthopnea and signs of acute left ventricular failure. Choking of the discs

* Dr. E. M. Landis kindly reviewed some of the serum protein data in this series.

was not present, but anasarca was marked. The edema cleared and the symptoms were entirely relieved in six days with 18 pounds loss of weight on an average daily intake of 3,000 c.c. With the diet protein at 40 grams and the daily loss of albumin in the urine ranging from 6 to 23 grams, the initial serum protein of 3.5 (1.3) grams rose in 48 hours to 5.2 (3.2) grams, the reversed albumin/globulin ratio becoming normal; on the seventh day the serum protein was 5.3 (3.2) grams. The hematocrit changed from 30 to 36 per cent, the CO_2CP from 47 to 46, the plasma chlorides from 627 to 598 mg., and the blood urea from 123 to 127 mg.

He was admitted again in October for the same complications. He cleared edema with a loss of 14 pounds of weight in four days on an average daily intake of 3,500 c.c. The serum protein of 5.5 (3.3) grams and the hematocrit of 30 per cent remained unchanged, the plasma chlorides changed from 660 to 610 mg., the blood urea ranged from 130 to 190 mg., and the CO_2CP, now low, changed only from 36 to 38 volumes per cent. It was increasingly difficult for him to take fluids or adequate amounts of food.

In January 1943 he was admitted in an obviously terminal state, with pulmonary infarction syndrome; bronchopneumonia developed on the fifth day, and he died on the ninth day.* No disturbing attempts were made to keep the intake high or to enforce the régime; yet, driven by fever and thirst, until two days before his death he took an average intake of 2,500 c.c. daily, and from 900 to 1,800 c.c. of urine were elaborated daily. Serum proteins were 4.8 (3.3) grams, rising to 5.8 (3.4) on the seventh day and dropping to 5.0 (3.2 grams) on the ninth day; and for the same days the hematocrit was 21, 25, and 29 per cent. The blood urea rose from 180 to 215 mg. before death and the plasma chlorides ranged from 594 to 605 mg.

The carbon dioxide combining power was 35.2 on this last admission and 36.8 volumes per cent on the fifth day; during his rapid failure in the last four days it dropped to 25.2 on the seventh day, and in spite of the administration of enough sodium chloride and sodium bicarbonate to increase markedly the moderate edema still present, it was only 28.3 volumes per cent on the ninth day. (In recent quantitative observations on a "dry" nephritic [D. C., age 26] given 60 grams of sodium salts in 48 hours on two different occasions, a carbon dioxide combining power of from 26 to 28 volumes per cent was not affected appreciably, although only one quarter of the extra salt given appeared in the urine; but edema was produced and dehydration became marked.)

A similar case (204), L. T., male, age 27 in 1938, was followed three years.† In *April 1938* the edema cleared completely with a 20 pound weight loss in 12 days on an average daily intake of 4,600 c.c. In *February 1940,* with a diet protein of 40 grams and an average daily intake of 4,500 c.c. he lost 10 pounds of weight in eight days while the edema cleared and the serum protein dropped from 4.4 (2.6) to 3.6 (1.6) grams, the hematocrit rising from 29 to 37 per cent. In the next 30 days, in spite of a daily loss of albumin in the urine of from 3 to 18 grams, and with the diet protein still held at 40 grams, the serum protein rose to 5.2 (2.6) grams, the hematocrit dropping to 32 per cent. The plasma chlorides ranged from 570 to 610 grams. Supplements of isotonic dextrose, totaling 2,000 c.c. daily, were given by vein for the first 10 days, yet, in spite of choked discs and retinal hemorrhages on admission, neither pulmonary edema nor convulsions were produced and there was actual improvement in vision as measured by a Snellen chart.

* Autopsy in brief: Multiple large pulmonary infarctions and superimposed bronchopneumonia; fresh pericarditis with 200 c.c. of fluid; heart grossly enlarged with marked atherosclerosis and calcification of the coronary vessels; fine droplets of fat dispersed throughout the hepatic parenchyma; "typical chronic glomerulonephritis" with involvement of the glomeruli varying from complete fibrosis to swelling and increased cellularity.

† Dr. George Dock confirmed the diagnosis and the effectiveness of the high fluid régime in this case.

Another case (*213*), R. T., male, age 19 in 1940, with severe subacute (glomerular) nephritis was admitted after 24 hours of vomiting. In the face of a maximum specific gravity of the urine of 1.010 (corrected for albumin) his daily intake for 18 days averaged 10,000 c.c., with a maximum intake for one day of 15,000 c.c., and a maximum urine output for one day of 18,000 c.c. In spite of this flood of water through him and his impaired kidneys, the plasma chlorides rose from 462 to 511 mg. without extra salt, and his massive edema cleared completely with a weight loss of 24 pounds in the first eight days.

Comment. The observations in this series confirm the notorious resistance to any type of therapy of "nephrotic edema," but indicate that it can be best controlled for a longer time on this high fluid régime, even on the pediatric service where the difficulties of enforcing such a régime are much greater.

With the frequent determinations of the plasma protein percentages it appeared that most of the percentage changes in the plasma proteins are relative and the result of swift fluctuations in the volume of the circulating blood.[20, 21, 25, 60] The studies with the low protein diets suggest that absolute plasma protein defects are more often due to faulty protein metabolism or exchange than to any protein "lack" in the diet or "loss" in the urine, and that such protein defects are corrected more readily, if subject to improvement at all, by some general improvement affecting, for example, liver function, than by a high protein diet.[26, 27, 28, 29]

It was also noted that laboratory determinations made from blood samples were often poor guides to salt replacement therapy, for the plasma chloride and carbon dioxide combining power percentages were often normal when salt was badly needed for *volume* replacement, or were low when extra salt, given in an attempt to correct sodium or chloride deficits in the face of marked impairment of renal function, led only to an increase in edema or to concentration of body-fluid with cellular dehydration. When the renal function was so badly impaired that the kidneys were unable to regulate the electrolyte pattern, the correction of these deficits was effected only by improvement of renal function, when that was possible.[1, 2, 3, 30, 31, 64]

It was noted that left ventricular failure and pulmonary edema and striking eye-ground changes and convulsions (figure 1, also) that had developed during a period of low fluid intake (and not infrequently develop even in non-edematous patients on a restriction of fluids) sometimes disappeared or were greatly improved when the high fluid intake, even with intravenous supplements, was enforced. This suggests that the syndromes of pulmonary, cerebral, and retinal edema are not directly related to the simple volume increase in interstitial fluid that we call edema, anasarca or dropsy, but may be more directly related to cell injury from cell anoxia or even cell dehydration, for example, which are common in serious illness.[2, 6, 31, 32, 33, 39, 40, 47, 58, 64]

In general, plasma protein, electrolyte and capillary bed disturbances were most effectively relieved, when correctible at all, by the minimum re-

quirement of salt and the maximum of plain water; thus, *plain water,* oxygen and small doses of adrenalin by their effect on cell function and circulating blood volume (presumably by improving renal and hepatic function and restoring the tone of the vascular bed) corrected these disturbances more often than large amounts of protein or salt, or a restriction of fluids.

Figure 8. A Case of Progressing Cardiovascular Disease, Managed on Restricted Fluid and High Fluid Régimes: The majority of patients are quite readily freed of their edema in almost any given period of treatment on either type of régime. The most significant observations in this study, therefore, are those which indicate that a high fluid intake régime can relieve edema which has not been relieved by a competently directed restricted fluid régime. (See V. J. B., figure 3, also.)

This case was followed closely for nearly five years, from an acute coronary occlusion until death. His course was marked by continuous unfavorable progress with increasing coronary, myocardial and renal insufficiency and, during the year on restricted fluids, by the development of nephrotic features. He was observed for almost three years on the high fluid régime, then, through the courtesy of an associate, for a year on a restricted fluid régime, and finally, for 10 months again on a high fluid régime.

Case 128. H. L. M., male, restaurant manager, age 45 in 1936. His father, 10 years after a hemiplegia, died at the age of 72; his mother was disabled by severe angina at age 65. The patient had anginal pain in December 1935 and ankle edema by the spring of 1936 when he had his first myocardial infarction, with an acute left ventricular failure and a drop in blood pressure from 190 mm. Hg systolic and 135 diastolic to 125 mm. systolic and 90 mm. diastolic, and the electrocardiographic changes of an acute infarction and an atypical left bundle branch block. By October 1937 physical, mental and alcoholic intemperance had brought his edema to the stage of general anasarca with hydrothorax and ascites, which were cleared at home in 12 days on a neutral diet with a measured intake of from 4 to 5 liters daily. Indiscretions induced frequent attacks of angina, left ventricular failure, and recurrences of edema; the latter he recognized by unusual weight gain and cleared by returning to his high fluid régime on his own initiative. With his digitalis he took ammonium chloride and diluted hydrochloric acid, but he found that these were not sufficient to prevent the recurrence of edema or effect its clearing without taking 4,000 c.c. or more of water daily. Until 1939 no mercurial diuretic was used.

The *January 1939 admission* illustrates management in the three years from May 1936 to April 1939. Peripheral edema extended along the abdominal wall and up the back to mid-scapula; bilateral hydrothorax and ascites were present, and the liver edge could be palpated at a hand's breadth below the costal margin. By the end of the first three days there was no weight loss in spite of evident marked loss of edema, as shown by the disappearance of peripheral edema and a marked decrease in the size of the abdomen (indicating a marked shift of water to the cells even during and following a preliminary rehydration weight gain which had amounted to two pounds by the morning of the second day). In the next eight days edema cleared entirely with a weight loss of 20 pounds on an average intake of 4,200 c.c. daily.

His usual indiscretions resulted by April 1939 in a recurrence of massive edema which persisted on a restricted fluid régime until March 1940. During these 11

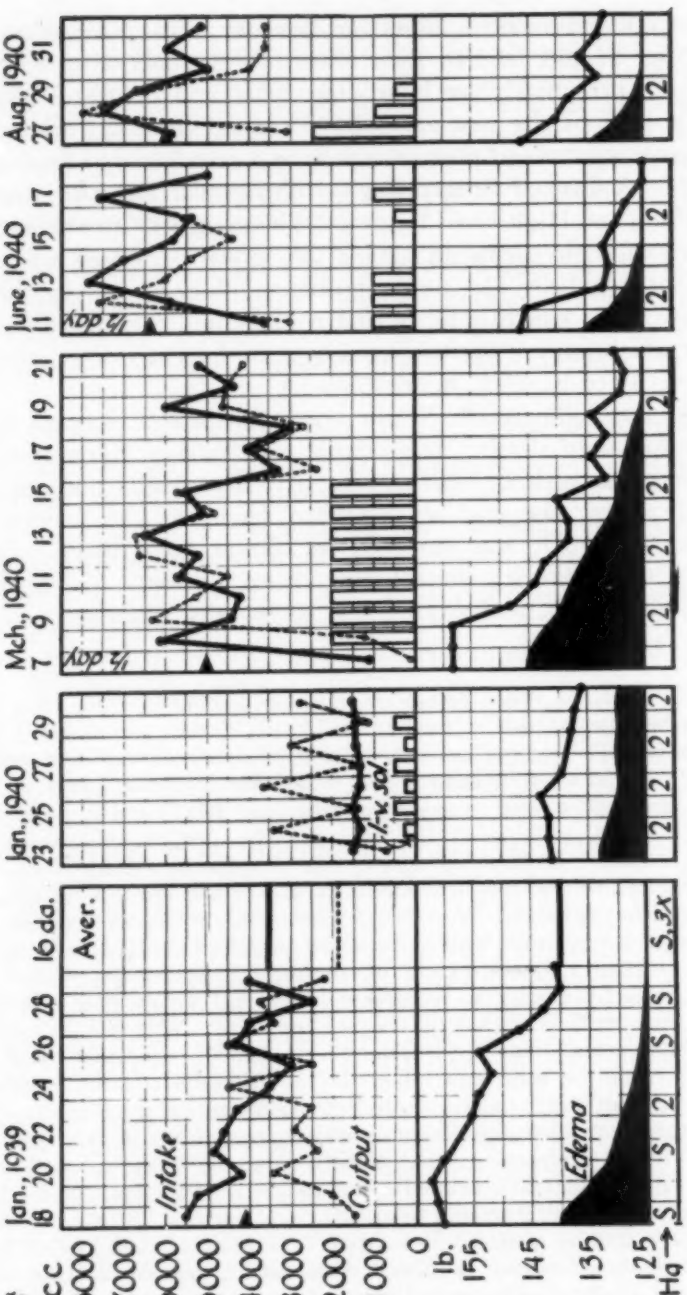


FIG. 8. A case of progressing cardiovascular disease managed on restricted fluid and high fluid régimes.

months he was disabled by anasarca in spite of seven months in the hospital and active treatment by competent internists with the usual measures; which included a sharp restriction of fluids with a low-salt, high-protein diet (120 grams), potassium nitrate, and hypertonic dextrose solutions with salyrgan or aminophyllin by vein. The brawny edema that reached to the waist and the ascites did not respond to therapy even though, for example, in August 1939 he received a diet protein of 140 grams daily with thrice weekly injections of salyrgan and there was a rise in the plasma proteins from 4.0 (2.3) to 5.4 (3.2) grams in 18 days.

The *January 1940 admission* at the Mayo Clinic illustrates the type of restricted fluid régime and intensive therapy used during this year. A few of the significant findings there, in addition to the anasarca and ascites, were: a blood pressure of 182 mm. Hg systolic and 140 mm. diastolic, a few retinal hemorrhages, a plasma protein determination of 6.5 (4.2) grams, albuminuria (grade 2), a blood urea of 50 mg. and a fixed specific gravity of the urine between 1.010 and 1.013. The diagnosis was "diffuse arterial disease with hypertension (group 3), severe myocardial damage and congestive heart failure," and the prognosis was given as "poor." The average daily intake was held at 1,500 c.c., including the hypertonic dextrose solutions, with salyrgan by vein every second day, and with aminophyllin on alternate days. A forced diuresis was evoked with some five pounds net weight loss, but there was very little change in the edema and no relief of his severe paroxysmal dyspnea and orthopnea.

In spite of the continuation of this régime through February the anasarca increased so that within two weeks after leaving there the aspiration of ascitic fluid was necessary, and within three weeks more, aspiration again seemed imperative.

The *March 1940 admission* shows the data of the two weeks' trial on the high fluid régime, requested by his attendant. The abdomen was tightly swollen with ascites and the liver edge was ballottable one finger's-breadth below the umbilicus; there was pitting edema of the abdominal wall and deep pitting up the back as high as the scapulae; bilateral hydrothorax was present. The tight brawny edema of the legs and thighs had been present continuously since April 1939. By the end of 36 hours he was much more comfortable, his thirst was relieved, the abdomen and peripheral edema had softened a little, and the pulmonary râles were decreased; which indicated, since there had been no weight loss, some shift of water to the thirsty cells. On the third day the first dose of mercupurin resulted in a diuresis and a weight loss which continued with two more doses of mercupurin until 28 pounds of weight had been lost in seven days on an average intake of over 5,000 c.c. daily, achieved by 1,000 c.c. supplements of 5 per cent dextrose in distilled water given twice daily. A test dose of mercupurin on the eleventh day eliminated the little occult edema that remained. At the request of his attendant, the diet protein of the neutral diet had been held at 130 grams daily, yet the plasma prpteins dropped from 5.8 (4.0) to 4.8 (3.2) grams in 13 days. The hematocrit changed only from 52 to 49 per cent, and the plasma chlorides rose from 528 to 595 mg.

The tight brawny edema and the ascites and hydrothorax were cleared completely for the first time in a year, and his symptoms were so well relieved and controlled that he resumed many activities during the next nine months. In that time he was admitted twice after lapses from his régime.

In the *June 1940 admission* he cleared 20 pounds of edema in seven days on an average daily intake of 6,700 c.c. With the diet protein at 65 grams, the plasma protein rose from 3.6 (2.4) to 4.8 (3.6) grams in two days and 5.3 (3.0) grams by the eighth day. (In August 1939 with the diet protein at 140 grams, there was a rise from 4.0 (2.3) to 5.4 (3.2) grams in 18 days, but without any loss of edema.) There was no evidence of body fluid dilution, the hematocrit readings for the same days being 39, 45, and 50 per cent, and the plasma chlorides 511, 561, and 610 mg.

In the *August 1940 admission* he cleared 15 pounds of edema in five days on an

average daily intake of 6,000 c.c. With the diet protein at 40 grams, the plasma proteins actually rose from 4.2 (2.8) to 5.3 (3.3) grams in the five days; the hematocrit rose from 40 to 52 per cent, and the plasma chlorides dropped from 590 to 544.

During his last four months he adhered to his régime and did not have to reenter the hospital; he spent from 10 to 12 hours a day at his restaurant before his sudden death at home late in December of 1940.*

Comment. Most of us have been taught to regard such brine-logged patients as water-logged and we can therefore appreciate Sir Thomas Witherly's [41] remarks on the case which he reported to the Royal College of Physicians about 1690: "A Wine-Cooper fell into a Dropsy which resisted all the usual Methods.† This Man was prodigiously swell'd, Belly, Back, Sides, Thighs and Legs. Being past all Hopes and having on him an inextinguishable Thirst, he was permitted to drink 14 Quarts of Water in about 10 Hours and in all that Time made not one drop of Urine. Soon after he began to piss; and he drank on, 4 or 5 Quarts daily, and so recovered. . . . That Water should expell Water is a Miracle beyond any of St. Winifred's. Now no Man in his Senses would have prescribed such a Water course to cure a Dropsy, which shows how little we know of Nature and the great Uncertainty of our Art."

Recapitulation

A high fluid intake was given, with the *proper* regulation of sodium, to edematous patients with:

Severe acute injury of the myocardium,
Marked narrowing or incompetence of the heart valves,
Advanced general vascular disease,
Eclampsia and preëclamptic toxemias and
Advanced nephritis with the nephrosis syndrome.

This was often in the face of high venous pressures or low plasma proteins, and even in spite of the presence on admission of such findings as:

Acute pulmonary edema,
Convulsions or choked discs,
Low fixed specific gravity of the urine or
Marked chloride or sodium deficits.

The common objections to a high fluid intake were not sustained by the observations, for clinically a large intake of plain water on this régime did not:

"Overwork" the heart or "overburden" the circulation,
Produce generalized edema or retard its disappearance,

* At autopsy the chief significant findings were: the greatly enlarged heart with marked sclerosis of the coronary vessels, multiple old myocardial infarctions with fibrosis and thinning of one area of the left ventricular wall. On sectioning the other organs, the knife felt as though it were passing through fine wet sand; diffuse arteriolar sclerosis was present in every organ, most advanced in the arterioles of the lungs and of the kidneys.

† The "usual methods" besides purges and vomits, included the use of calomel, mineral acids and the muriate of ammonia, but not a free use of water, even from Winifred's Well.

Act adversely with high venous pressure or low plasma proteins,
Produce pulmonary edema or convulsions,
Produce so-called "water intoxication" (body fluid dilution),
"Wash out" *needed* sodium or chloride, or
Hinder restoration to normal of lost body fluid volume or
The correction of electrolyte pattern defects.

On the contrary, it was observed that such cases and such conditions tolerated the large amounts of water of the régime without disaster and with immediate and late results superior to those obtainable on accepted restricted fluid régimes.

Summary

1. The effects of a régime, in which a very high fluid intake was enforced, on patients with edema and cardiac disease are reported, as observed and studied for eight years in 626 separate periods of treatment of 402 cases. The method used in the study is outlined, the material is analyzed, and some of the general and specific observations are presented.

2. It was observed that patients with marked edema, particularly the 94 per cent with gross cardiopathy, tolerated the high fluid intake with impunity and that the results were better than those formerly obtained with the restriction of fluids.

3. It is suggested that the régime used is physiologically sound and that it is clinically useful in the correction and prevention of the intimately related phenomena of edema, oliguria or anuria and dehydration, wherever they are encountered or anticipated.

4. The observations appear to call for a critical reëxamination of the accepted clinical practice of the restriction of fluids in the presence of edema, and of the accepted hypotheses regarding edema formation and congestive heart failure upon which this practice is based.

APPENDIX

Analysis of Material *

Table IV

Primary Disease Groups	Gross Edema	No Gross Edema	Totals
Arteriosclerotic and hypertensive heart disease	83	51	134
Acute myocardial infarction	40	59	99
Advanced general vascular disease with cardiopathy	21	4	25
Cor pulmonale and thyrogenic heart disease	10	11	21
Rheumatic heart disease, chronic valvular	48	22	70
Nephritic syndromes	23	3	26
Miscellaneous cases with edema and/or cardiopathy	16	11	27
Total number of cases	241	161	402

* Table 3, which listed all of the 402 cases of this series and showed the data most pertinent to this study from 575 of the 626 separate periods of observation, is omitted here for lack of space and paper. (It will be included with the reprints.) Its data are summarized in tables 1 and 2 above and in the tables below.

The cases in the second line are arbitrarily separated from those in the first line, and there were 15 more patients with acute myocardial infarction in the other groups. In the advanced general vascular disease group are included seven cases of malignant hypertension. The rheumatic heart disease cases include 12 with acute rheumatic pancarditis and four with subacute bacterial endocarditis (*Streptococcus viridans*). The nephritic syndromes included were not mild, 20 of the 26 showed evident cardiopathy, and 10 fulfilled the ordinary criteria for nephrosis. In the 11 miscellaneous cases with no gross edema there were three with congenital heart disease (a patent ductus arteriosus, a coarctation of the aorta, and a dextrocardia, with bundle branch block), and two toxemias of pregnancy; the 16 cases with gross edema are described further in table 6.

TABLE V

Some Complications Which Tolerated the Régime

Findings	Instances
Retinal edema and/or hemorrhages	38
Advanced retinitis with choked discs	16
Major convulsions	11
Acute left ventricular failure or pulmonary infarction	36
Acute profuse pulmonary edema	18
A maximum specific gravity of the urine below 1.016	51

These findings were present at the time of admission. Retinal edema with or without hemorrhages was present 15 times, and fresh retinal hemorrhages 32 times. In addition, retinal sclerosis with old hemorrhages was noted 24 times. In the 16 patients with choked discs, the visual acuity in seven actually improved. The 11 admitted with major convulsions recovered without recurrences; four were eclamptics. In addition, 17 patients with Adams-Stokes attacks and 29 admitted following cerebral accidents (including four with meningeal hemorrhage and xanthochromic spinal fluid) were treated; and seven other cases admitted after arterial emboli cleared edema. (Emboli occurred twice during treatment in patients who were fibrillating.)

Acute left ventricular failure was present in 12 instances, gross profuse hemoptyses in 10, and the syndrome of pulmonary infarction in 24 instances. Acute pulmonary edema with the profuse expectoration of thin bloody froth was present on admission in 18 instances and improvement was not retarded by the generous intake of fluid. Pulmonary edema occurred three times during therapy (see Untoward Reactions). In addition, in 37 instances hydrothorax reaching to mid-scapula was cleared completely without aspiration.*

* Hydrothorax was aspirated only 10 times in the 393 periods of treatment; in three for bloody effusion in rheumatic fever and in two for diagnostic purposes. Ascitic fluid was aspirated only nine times; in three of these instances before therapy was started. Thus, aspiration for either was done for relief of symptoms after therapy was begun, only 11 times in the eight years of the study.

In 51 instances the maximum specific gravity of the urine was below 1.016, as determined on admission when dehydration and oliguria were marked or later by a concentration test. (In such cases the daily intake was held at about 5 liters to insure about 3 liters of urine-water.[1]) Marked oliguria or anuria was encountered 53 times with acute myocardial infarction; nine patients with only one kidney (three newly operated) and two cases of advanced bilateral congenital hydronephrosis tolerated the régime well. Of 41 patients admitted in severe uremia about half responded well, usually with large intravenous supplements (in some a blood urea of over 300 mg. became normal).

Other conditions which served to test the régime were: auricular fibrillation and/or flutter in 73 cases; both mitral stenosis and aortic insufficiency in 19; either mitral stenosis or aortic insufficiency in 60; heart block complete and permanent in 12; pregnancy beyond the first trimester in 16, and a major operation during the period of observation in 21.

Table 6 indicates to what extent the effect of the régime was observed on the more resistant forms of edema, not infrequently in the face of a rapidly fatal outcome from the primary disease. The average ages and the sex incidence for the various groups were characteristic of any similar series.

TABLE VI

Groups of the 241 Cases with Gross Edema

		Main Groups			
		Cases	Male	Female	Average Age
Simple hypertensive and arteriosclerotic heart disease	70				
Acute myocardial infarction	40				
Resistant ascites, with cardiopathy	13				
Advanced general vascular disease	11				
Diabetes mellitus with anasarca	10				
Cor pulmonale (7), Thyrogenic ht. dis. (3)	10				
Heart Disease, Degenerative, Progressive	Totals	154	84	70	60.9 yrs.
Mitral stenosis and/or aortic insufficiency	38				
Same, with acute rheumatic pancarditis	6				
Same, with viridans endocarditis	4				
Heart Disease, Rheumatic, Chronic Valvular	Totals	48	14	34	41.6 yrs.
Nephrosis	10				
Acute and subacute nephritis	13				
Eclampsia (5), lymphoblastoma (5), pernicious anemia (3), other cases (3)	16				
Renal Disease and Other Cases	Totals	39	19	20	34.0 yrs.
Gross Edema Cases	Totals	241	117	124	52.5 yrs.

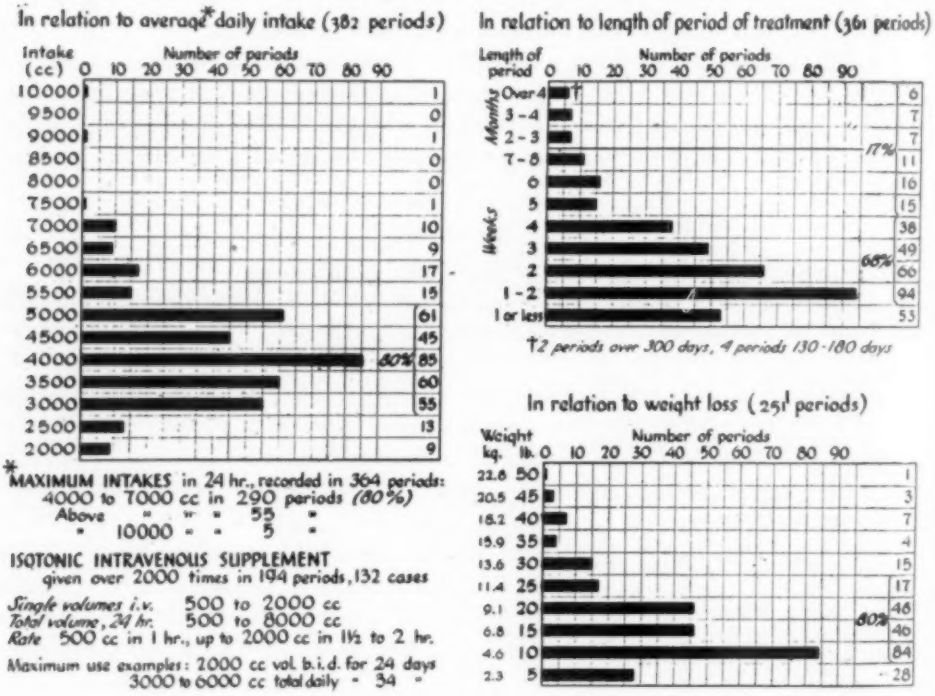
The 13 cases with resistant ascites had features of cirrhosis of the liver in addition to cardiopathy; all had been aspirated before admission, some repeatedly; their livers were very large or very small, and there was a history of alcoholism in nine of the 12 men. The average age for the ad-

vanced general vascular disease group was only 41 years; three of these had the syndrome of malignant hypertension. The 10 cases with diabetes mellitus had had their self-neglected diabetes for from nine to 20 years and had developed the peculiarly resistant anasarca with nephrotic features common to such cases (average age 54.4 years, 10 years less than the average age for the first three sub-groups).

In the rheumatic heart disease group, edema and pleural effusions were controlled in six cases of acute pancarditis, and edema was controlled in four cases dying of subacute bacterial endocarditis (proved at autopsy or by blood cultures of *Streptococcus viridans*).

TABLE VII

Frequency Distribution of 393 Periods of Treatment in 241 Cases with Gross Edema



In some of the 10 cases that showed the resistant edema and the accepted criteria of nephrosis low-protein diets were used. The 13 acute and subacute nephritis cases were all very ill and had azotemia; nine had gross cardiopathy, and five "smokey" urine. All the 16 miscellaneous cases cleared marked edema, one had multiple myeloma and one had carcinomatosis with ascites (adenocarcinoma by biopsy).

The average daily intake recorded was from 3,000 to 5,000 c.c. in 306 periods or 80 per cent, and from 5,500 to 7,500 c.c. in 52 periods or 13 per

cent. The *maximum* intake in 24 hours (usually ingested in less than 12 hours) was recorded in 364 periods; 4,000 to 7,000 c.c. in 80 per cent and over 7,000 c.c. in 60 periods or 16 per cent. Isotonic intravenous supplements were given as summarized in the lower left corner of the table.

The lengths of the periods of treatment recorded were from one to four weeks in 68 per cent and over five weeks in 17 per cent; the 15 patients on the régime for from three months to a year showed no evidence of body fluid disturbance.

In 251 periods it was possible to record the edema weight loss, which was from 10 to 25 pounds in 193 periods or 80 per cent, and from 30 to 50 pounds in 30 periods or 15 per cent. Some patients lost edema-weight equal to 50 per cent of their edema-free body weight (figure 3, W. T.). The weight losses recorded are corrected for tissue-weight loss. (It should be recalled that in a dehydrated edematous patient, a shift of water between the cells and extracellular fluid of such magnitude may occur that, with the same degree of edema cleared, one patient may lose 10 pounds, another 20 pounds of weight.)

The analyses of the data from the 161 cases with "no gross edema" similar to those in tables 6 and 7, are not presented here since they do not appreciably affect the statistics for the whole series of 402 cases.

Acknowledgments. It was possible to begin and pursue this study only through the generous coöperation and active assistance of the author's associates in the several departments of the Great Falls Clinic. The dietitians of the Montana Deaconess and Columbus Hospitals, and the chief laboratory technician and the nursing staff of the Montana Deaconess Hospital were most helpful. The study benefited particularly by the constant and intelligent efforts of Edith Qualls, R.N., supervisor of the Medical floor since 1936.

The author wishes to thank H. A. Schroeder, E. M. Landis, L. Eichelberger, F. A. Coller, C. C. Sturgis, F. D. Johnston and T. J. Dry for opportune discussion, criticism, or encouragement; and particularly L. H. Newburgh, whose work on the edema of nephritis inspired this study, and to whom the author is indebted for helpful criticism in 1936 and 1939.

BIBLIOGRAPHY

1. Newburgh, L. H., and Lashmet, F. H.: A comparative study of the excretion of water and solids by normal and abnormal kidneys, Jr. Clin. Invest., 1932, xi, 1003–1009.
2. Newburgh, L. H., and Lashmet, F. H.: The importance of dealing quantitatively with water in the study of disease, Am. Jr. Med. Sci., 1933, clxxxvi, 461–470.
3. Freyberg, R. H., and Lashmet, F. H.: A quantitative study of renal injury in a case of acute poisoning by bichloride of mercury with a note regarding treatment, Am. Jr. Med. Sci., 1935, clxxxix, 392–399.
4. Newburgh, L. H., and MacKinnon, F.: The practice of dietetics, 1934, The Macmillan Co., New York, pp. 7–20, 86–97, 225–244, 253–258.
5. Addis, T.: The osmotic work of the kidneys and the treatment of glomerular nephritis, Trans. Assoc. Am. Phys., 1940, lv, 223–229.
6. Coller, F. A., and Maddock, W. G.: A study of dehydration in humans, Ann. Surg., 1935, cii, 947–960.

7. Coller, F. A., and Maddock, W. G.: Water and electrolyte balance, Surg., Gynec., and Obst., 1940, lxx, 340–354.
8. Nadal, S. W., Pedersen, S., and Maddock, W. G.: Two contrasting types of dehydration, Univ. Hosp. Bull., Ann Arbor, 1941, vii, 53–55.
9. Starling, E. H.: The fluids of the body, 1900, W. T. Keener & Co., Chicago, pp. 152/154, pp. 163–164, pp. 175–177.
10. Darrow, D. C., and Yannet, H.: The changes in the distribution of body water accompanying increase and decrease in extracellular electrolyte, Jr. Clin. Invest., 1935, xiv, 266–275.
11. Hastings, A. B., and Eichelberger, L.: Exchange of water and salt between muscle and blood, Jr. Biol. Chem., 1937, cxvii, 73–93. *Ibid.*: 1937, cxviii, 197–218.
12. Gamble, J. L.: Extracellular fluid, Bull. Johns Hopkins Hosp., 1937, lxi, 151–197.
13. Best, C. H., and Taylor, N. B.: The physiological basis of medical practice, 1937, Wm. Wood, Baltimore.
14. Goodman, L., and Gilman, A.: The pharmacological basis of therapeutics, 1941, The Macmillan Co., New York.
15. Milbert, A. H.: Infusion reactions with special reference to "speed shock," Am. Jr. Surg., 1934, xxvi, 479–485.
16. Warthen, H. J.: Massive intravenous injections, Arch. Surg., 1935, xxx, 199–227.
17. Cutting, R. A., et al.: Cause of death resulting from massive infusions of isotonic solutions, Arch. Surg., 1939, xxxviii, 599–616.
18. Smyth, F. S.: Studies in so-called water intoxication, Jr. Clin. Invest., 1930, xii, 55–65.
19. Cope, C. L.: Alkali poisoning (Abst.), Jr. Am. Med. Assoc., 1937, cviii, 336.
20. Warren, J. V., Merrill, A. J., and Stead, E. A., Jr.: The role of extracellular fluid in the maintenance of a normal plasma volume, Jr. Clin. Invest., 1943, xxii, 635–641.
21. Seaman, B. W., and Ponder, E.: The estimation and control of post-operative dehydration with the aid of hemoglobin and plasma protein determinations, Jr. Clin. Invest., 1943, xxii, 673–685.
22. Landis, E. M.: Vascular physiology and clinical medicine, Ann. Int. Med., 1936, x, 290–298.
23. Peters, J. P., et al.: Total acid base equilibrium of plasma in health and disease, X, Acidosis of nephritis, Jr. Clin. Invest., 1929, vi, 517.
24. Moore, N. S., and Stewart, H. J.: Variation of specific gravity of plasma of blood and the means available for altering it, Jr. Clin. Invest., 1930, ix, 423.
25. Stewart, H. J.: Mechanism of diuresis; alterations in specific gravity of blood plasma with onset of diuresis in heart failure, Jr. Clin. Invest., 1941, xx, 1–6.
26. Whipple, G. H.: Protein production and exchange in the body, including hemoglobin, plasma protein and cell protein, Am. Jr. Med. Sci., 1938, cxcvi, 609–621.
27. Stadler, H., and Stenger, D.: A case of Pick's syndrome as the basis for a study of hypoproteinemia, Jr. Pediat., 1941, xviii, 84–94.
28. Jacobson, S. D.: The effect of phlebotomy on the blood volume, read at the meeting of The American Federation for Clinical Research, Chicago, Nov. 4, 1943 (unpublished).
29. Lyons, R. H., Jacobson, S. D., and Neerkin, J.: The relationship between changes in the plasma volume and changes in the hematocrit and serum protein concentrations, Proc. Central Soc. Clin. Res., 1943, xvi, p. 17.
30. Rowntree, L. G., et al.: The effects of experimental passive congestion in renal function, Arch. Int. Med., 1913, xi, 120–147.
31. Toth, L. A.: Urine excretion during anoxia from normal and denervated kidneys in dogs with and without adrenal glands, Am. Jr. Physiol., 1940, cxxix, 532–538.
32. Landis, E. M.: Micro-injection studies of capillary permeability: III. The effect of lack of oxygen on the permeability of the capillary wall to fluid and to plasma proteins, Am. Jr. Physiol., 1928, lxxxiii, 528.

33. Cusick, P. L., Benson, O. O., Jr., and Boothby, W.: Effect of anoxia and high concentration of oxygen on the retinal vessels, Proc. Staff Meet. Mayo Clin., 1940, xv, 500.
34. Altschule, M. D., and Blumgart, H. L.: The circulatory dynamics in tricuspid stenosis, Am. Heart Jr., 1937, xiii, 589–598.
35. Wiggers, C. J.: Cardiac adaptations in acute progressive anoxia, Ann. Int. Med., 1941, xiv, 1237–1247.
36. Poll, D., and Stern, J. E.: Untoward effects of diuresis (with special reference to mercurial diuretics), Arch. Int. Med., 1936, lviii, 1087–1094.
37. Tyson, M. C.: Danger of intravenous mercurial injections in nephrosis, Jr. Am. Med. Assoc., 1941, cxvii, 998–999.
38. Dick, M. W., Warweg, E., and Andersch, M.: Acacia in the treatment of nephrosis, Jr. Am. Med. Assoc., 1935, cv, 654–657.
39. Wilson, D. M., and Sunderman, F. W.: Studies in serum electrolytes; XII. The effect of water restriction in a patient with Addison's disease receiving sodium chloride, Jr. Clin. Invest., 1939, xviii, 35.
40. Anderson, W. A. D., and Bethea, W. R.: Renal lesions following the administration of hypertonic solutions of sucrose, Jr. Am. Med. Assoc., 1940, cxiv, 1938.
41. Witherly, Sir Thomas, cited in Sir John Floyer and Edw. Baynard's History of cold bathing both ancient and modern (4th ed.), 1715, Wm. Innys, London, ii (Baynard), pp. 449–454.
42. Baker, Sir George: Medical transactions, 1772, ii (Article xvii), p. 235, published by the Royal College of Physicians.
43. Withering, William: An account of the foxglove (1785) in the miscellaneous tracts, 1822, Longman, et al., London, ii, p. 127, 137, 287 and 289.
44. Milman, Sir Francis: Animadversions on the nature and cure of the dropsy, 1786, J. Walker, London, p. 122.
45. Darwell, John: Dropsy, in John Forbes' "Cyclopedia of practical medicine," 1845, Lea and Blanchard, Philadelphia, p. 720.
46. Flint, Austin: In Napheys' Modern medical therapeutics (5th ed.), 1878, D. A. Brinton, Philadelphia, p. 418.
47. Flint, Austin: A treatise on the principles and practices of medicine (6th. ed.), 1886, Lea Bros. and Co., pp. 33, 64: 873.
48. Osler, W.: Principles and practice of medicine (2nd. ed.), 1896, D. Appleton, New York, p. 787.
49. Christian, H. A.: In Osler's Principles and practice of medicine, 1938, D. Appleton Century Co., New York, p. 1036.
50. Levine, S. A.: Clinical heart disease, 1936, W. B. Saunders, Philadelphia, pp. 301–302.
51. Farr, L. E.: Conference on therapy; treatment of edema, Jr. Am. Med. Assoc., 1939, cxii, 837–843.
52. Willius, F. A.: Regulation of diet in heart disease, Proc. Staff Meet. Mayo Clin., 1936, xi, 202–206.
53. Binger, M. W.: General treatment of edema, Proc. Staff Meet. Mayo Clin., 1936, xi, 648–650.
54. Binger, M. W.: Edema (editorial), Ann. Int. Med., 1941, xv, 617.
55. Lehnhoff, H. J., and Binger, M. W.: Treatment of edema of renal origin, Jr. Am. Med. Assoc., 1943, cxxi, 1321–1325.
56. Dry, T. J.: Congestive heart failure: Factors influencing the ultimate prognosis, Jr. Am. Med. Assoc., 1942, cxviii, 263–266.
57. DeSnoo, K.: The prevention of eclampsia, Am. Jr. Obst. and Gynec., 1937, xxxiv, 911–939.
58. McPhail, F. L.: The toxemias of pregnancy, Jr. Am. Med. Assoc., 1938, cxi, 1894–1897.

59. McPhail, F. L.: Water exchange in toxemias, West. Jr. Surg., Obst. and Gynec., 1939, xlvii, 306–317.
60. Chesley, Leon C., and Annitte, John E.: A study of salt restriction and of fluid intake in prophylaxis against pre-eclampsia in patients with water retention, Am. Jr. Obst. and Gynec., 1943, xlv, 961–971.
61. Goodman, J. I., and Corsaro, J. R.: The basal weight level in the treatment of congestive heart failure, Am. Heart Jr., 1943, xxvi, 338–342.
62. Schroeder, H. A.: Personal communication, 1939.
63. Schroeder, H. A.: Studies on congestive heart failure. I. The importance of the restriction of salt as compared to water, Am. Heart Jr., 1941, xxii, 141–153.
64. Schroeder, H. A., and Futcher, P. H.: Studies on congestive heart failure. II. Impaired excretion of sodium chloride, Am. Jr. Med. Sci., 1942, cciv, 52–62.
65. Jacobson, S. D., Leichtentritt, B., and Lyons, R. H.: The effect of acid and alkaline salts on some patients with rheumatoid arthritis, Am. Jr. Med. Sci., 1942, cciv, 540–546.
66. Pelner, L.: The rapid removal of excess joint fluid by acid salts, Am. Jr. Med. Sci., 1943, ccvi, 498–503.
67. Schemm, F. R.: A high fluid intake in the management of edema, especially cardiac edema. I. The details and basis of the régime, Ann. Int. Med., 1942, xvii, 952–969.
68. Schemm, F. R.: The loss of edema without loss of weight, read at the Meeting of The American Federation for Clin. Research, Chicago, Nov. 4, 1943 (unpublished).
69. Connell, W. F.: (Ontario) Personal communication, 1943.
Askey, J. M.: (California) Personal communication, 1943.
Kurtz, C. M.: (Wisconsin) Personal communication, 1943.
Lyon, R.: The Schemm treatment of chronic heart failure with edema, Jr. of Med. Assoc. of Alabama, August, 1944.*
70. Warren, J. V., and Stead, E. A., Jr.: Fluid dynamics in chronic congestive heart failure, Arch. Int. Med., 1944, lxxiii, 138–147.
71. Stead, E. A., Jr.: Care of the patient with chronic heart disease, Med. Clin. of North America, 1944, xxviii, 381–387.

* The Lyon reprint available to me does not give volume or page number.—[Author.]

THE LEUKOCYTE COUNT IN PRIMARY ATYPICAL PNEUMONIA OF UNDETERMINED ETIOLOGY *

By Ovid O. Meyer, F.A.C.P., and Ethel W. Thewlis,
Madison, Wisconsin

Bronchopneumonia of the type now commonly considered to be virus pneumonia was seen as long ago as 1872,[1] but present day attention was directed to it by much later reports, chiefly those of Gallagher,[2] Bowen,[3] Reimann,[4] Kneeland and Smetana,[5] and Longcope.[6] In recent years, probably because of greatly increased incidence and, to a lesser extent, proper recognition of this condition and the more positive exclusion of pneumonias of other types by detailed bacteriologic study, these atypical pneumonias have been very frequently observed. In the past six years more than a hundred reports relating to this condition have appeared in the literature.

It is generally believed that the disease, perhaps not an entity,[1] is of virus etiology, although this hypothesis has not been established. Stokes, Kenney and Shaw [7] and Francis and Magill [8] obtained an infectious agent that produced pulmonary lesions in ferrets and mice, but the agent could not be retained. Weir and Horsfall [9] have isolated in the mongoose a filterable agent obtained from patients with acute pneumonitis. Dingle and Finland [1] maintain that the matter of etiology is still unsettled.

The diagnosis of primary atypical pneumonia is difficult and at present rests entirely upon clinical and, in particular, radiologic criteria; and upon the exclusion of other types of bronchopneumonia of established bacteriologic etiology. The recent demonstration of the development of cold agglutinins in primary atypical pneumonia by Peterson, Ham and Finland [10] and Turner [11] may be of further help. Recognizing that another easily detectable condition would be useful in diagnosis, we made a careful and detailed study of the leukocyte formula.

The literature contains references to the blood findings in primary atypical pneumonia, but many of them are cursory remarks and they are not all in agreement. Several [1, 4, 12] indicate that the total leukocyte count is normal but may be elevated as the patient recovers. Some [3, 6, 13, 14] report a leukopenia. Some physicians have been under the impression that lymphocytosis is common, but there are no data in the literature to substantiate this. Goodrich and Bradford [15] report that the neutrophiles are normal, as is the total leukocyte count usually, whereas Reimann [4] and Yale and Smetana [5] observed an increase in neutrophiles with a normal total count. Middleton [16] has noted a monocytosis of 10 to 18 per cent.

* Received for publication December 31, 1943.
From the Department of Medicine, University of Wisconsin.
This study was aided in part by a grant from the Wisconsin Alumni Research Foundation.

The present investigation was made upon young adults ill in the Infirmary of the Student Health Service of the University of Wisconsin during the fall, winter and spring of 1942–1943. They comprised University students, civilians, sailors and Waves. The studies are divided into two groups. The first consists of 35 cases in which the diagnosis had already been made and roentgenographic evidence was decisive. As these were, therefore, relatively advanced cases, counts were made on another group of students with respiratory infection as soon as they were admitted to the hospital. Many of these did not develop pneumonia and were dropped, but 15 ultimately developed primary atypical pneumonia, and their blood was also studied thrice weekly or oftener until they left the hospital. Most of the patients had mild or moderately severe disease. No attempt is made here to separate these from the three severe cases, although it was recognized that the latter were more prone to have leukocytosis and marked increases in neutrophiles.

Methods

Complete blood counts and hematocrit determinations were made upon each patient at the time he or she was seen, Wintrobe tubes being used for this purpose. Thereafter total and differential leukocyte counts were done thrice weekly or oftener until the patient was discharged as well. The total counts were done in duplicate and the differential count of 500 cells was made from cover slip smears stained with Kingsley's stain. The pipettes and counting chamber were standardized by the U. S. Bureau of Standards.

Table I (35)

The Initial Leukocyte Counts of 35 Cases of Primary Atypical Pneumonia

No significant changes occurred in the basophiles and they are omitted from the table.

W.B.C. Thousands	No.	N.%	No.	L.%	No.	E.%	No.	M.%	No.
2,500–5,000....	1	40–45	1	5–10	3	0–4	25	0–4	
5,001–7,500....	9	46–50	2	11–15	7	5–8	9	5–8	9
7,501–10,000...	14	51–55	2	16–20	14	9–12	1	9–12	14
10,001–12,500..	6	56–60	3	21–25	6			13–16	9
12,501–15,000..	2	61–65	3	26–30	2			17–20	3
15,001–17,500..	2	66–70	14	31–35	2				
17,501–20,000..	1	71–75	6	36–40	1				
		76–80	2						
		81–85	2						
		86–90	1						

N.—Neutrophiles. E.—Eosinophiles.
L.—Lymphocytes. M.—Monocytes (large mononuclear cells).

Results. The results of the first counts of the 35 cases are shown in table 1. These may be summarized as follows: Leukopenia is rare, but a normal leukocyte count, range of 5 to 10,000, is the rule, having occurred in 23 (66 per cent) of the 35. An increase in neutrophiles at the expense of the lymphocytes is also usual. In 25 (71 per cent) the neutrophiles numbered more

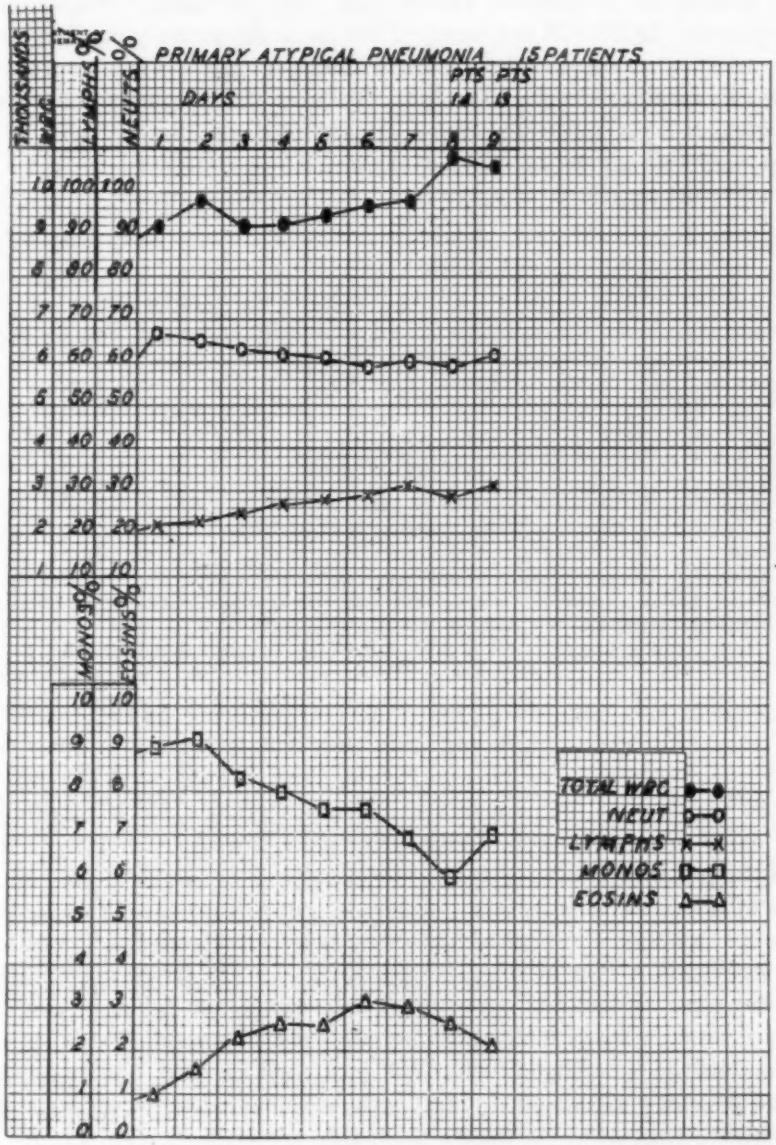


CHART 1. The averages of daily total and differential counts on 15 patients with primary atypical pneumonia. The first counts were done at the very onset of the illness. The basophiles and atypical cells, because of their rarity, are not included.

than 65 per cent of the cells. The lymphocytes were decreased to less than 25 per cent in 30 (86 per cent) of the 35 cases. The eosinophile count was usually normal or subnormal, but in nine (26 per cent) eosinophilia was demonstrated. In 26 (74 per cent) of the cases the monocytes (large mononuclear cells) were increased to more than 8 per cent. There were no significant abnormalities in the basophile count, nor any significant numbers of pathological cells. Hence they were ignored in compiling the table.

The results of the group of 15 cases which were observed from the onset of their disease are shown in table 2.

TABLE II (15)

The Initial Leukocyte Counts of 15 Cases of Primary Atypical Pneumonia
No significant changes occurred in the basophiles and they are omitted from the table.

W.B.C. Thousands	No.	N.%	No.	L.%	No.	E.%	No.	M.%	No.
2,500–5,000....	2	50–55	1	10–15	2	0–4	15	0–4	0
5,001–7,500....	5	56–60	2	16–20	3	5+		5–8	8
7,501–10,000...	4	61–65	3	21–25	7			9–12	4
10,001–12,500..	1	66–70	6	26–30	1			13–16	2
12,501–15,000..	2	71–75	1	31–35	1			17–20	1
15,001–17,500..		76–80		36–40	1				
17,501–20,000..		81–85	2						
20,001–22,500..	1								

N.—Neutrophiles. E.—Eosinophiles.
L.—Lymphocytes. M.—Monocytes (large mononuclear cells).

Analysis of this table shows that nine (60 per cent) of the 15 cases had normal total leukocyte counts and only two had leukopenia. In nine (60 per cent) neutrophiles were increased above normal (above 65 per cent) and in 12 (80 per cent) a lymphopenia was demonstrated. None of this group studied early showed an eosinophilic count above normal. Seven, or almost half, of the patients showed a distinct monocytosis, i.e. above 8 per cent.

The tables reveal that in several respects the findings are the same for the two groups, namely, the normal leukocyte count, neutrophilia, lymphopenia, and monocytosis. The increase in monocytes is less frequent in the early cases, however. Eosinophilia occurs in late cases, but never in early ones. There are no significant differences between the two groups with respect to the frequency of a normal total count, neutrophilia, and lymphopenia, but there is a greater percentage of severe lymphopenias, and marked increases in neutrophiles in the cases of longer standing.

As these patients improved and became afebrile certain changes in the blood formulae were noted which do not appear in the tabulated data. Briefly stated these were as follows: As the patient began to improve and became well (afebrile), there was usually an increase in the total leukocyte count, to above normal levels in half of the cases; a decrease in the neutrophiles and an increase in lymphocytes; a decrease in the eosinophiles,

whether above normal or not, in the older cases, and increases from low levels in the newer cases; and a subsidence of the abnormally high monocyte count in nearly all instances.

Discussion

In this investigation we have attempted to depict the abnormalities in the leukocyte picture which attend primary atypical pneumonia of undetermined etiology and to correct some erroneous concepts regarding the blood findings. Briefly, one may state that typically at the onset and even after the disease is well established, the leukocyte count is normal; there is an increase in neutrophiles, monocytes, and, in a fourth of the cases, eosinophiles. Coincidentally, a decrease in the lymphocytes is the rule. These findings apply to most cases but not to all. It appears that the finding having most significance as a possible aid in diagnosis is the very appreciable increase in monocytes which occurs in half the early cases and in three-fourths of those more advanced.

We have not done counts on a control series of pneumococcal pneumonias, but it is well known that leukocytosis with an increase in neutrophiles is the usual finding. In influenzal pneumonia and in psittacosis, leukopenia is the rule. In lobar pneumonia a transient monocytosis occasionally accompanies the beginning of resolution.[17] Occasionally a "post-infectious eosinophilia" follows the crisis in lobar pneumonia.[18] Presumably these conditions might occur occasionally in pneumococcal bronchopneumonia too, but apparently they are exceptional.

The findings here reported may prove to be of some aid in the diagnosis of primary atypical pneumonia, but they are not specific enough to justify a categorical statement. They may, however, serve to correct any misconceptions regarding the leukocytic response in primary atypical (virus) pneumonia of undetermined etiology.

Conclusions

1. Careful hematologic studies have been made in 50 cases of primary atypical (virus) pneumonia.

2. It was found that the leukocyte count was usually normal, and that the neutrophiles and monocytes increased. A lymphopenia was usually present. In 26 per cent of the cases in which the disease was somewhat advanced, there was eosinophilia at the time the first counts were made, but not in any of the cases where initial counts were made at the very onset of the pneumonia.

3. The leukocyte findings may be of some diagnostic aid but they are not necessarily conclusive.

BIBLIOGRAPHY

1. Dingle, J. H., and Finland, M.: Virus pneumonias. II, Primary atypical pneumonias of unknown etiology, New England Jr. Med., 1942, ccxxvii, 378.
2. Gallagher, J. R.: Broncho-pneumonia in adolescence, Yale Jr. Biol. and Med., 1934, vii, 23. Acute pneumonitis—a report of 87 cases among adolescents, Yale Jr. Biol. and Med., 1941, xiii, 663.
3. Bowen, A.: Acute influenza pneumonitis, Am. Jr. Roentgenol., 1935, xxxiv, 168.
4. Reimann, H. A.: An acute infection of the respiratory tract with atypical pneumonia, Jr. Am. Med. Assoc., 1938, cxi, 2377.
5. Kneeland, Y., Jr., and Smetana, H. F.: Current broncho-pneumonia of unusual character and undetermined etiology, Bull. Johns Hopkins Hosp., 1940, lxvii, 229.
6. Longcope, W. T.: Bronchopneumonia of unknown etiology (variety X), Bull. Johns Hopkins Hosp., 1940, lxvii, 268.
7. Stokes, J., Jr., Kenney, A. S., and Shaw, D. R.: A new filtrable agent associated with respiratory infections, Trans. and Studies Coll. Phys. Philadelphia, 1939, vi, 329.
8. Francis, T., and Magill, T. P.: An unidentified virus producing meningitis and pneumonitis in experimental animals, Jr. Exper. Med., 1938, lxviii, 147.
9. Weir, J. M., and Horsfall, F. L., Jr.: The recovery from patients with acute pneumonitis of a virus causing pneumonia in the mongoose, Jr. Exper. Med., 1940, lxxii, 595.
10. Peterson, O. L., Ham, J. H., and Finland, M.: Cold agglutinins (autohemagglutinins) in primary atypical pneumonia, Science, 1943, xcvii, 167.
11. Turner, J. C.: Development of cold agglutinins in atypical pneumonia, Nature, 1943, cli, 419.
12. Campbell, T. A., Strong, P. S., Grier, G. S., III, and Lutz, R. J.: Primary atypical pneumonia. A report of two hundred cases at Fort Eustis, Virginia, Jr. Am. Med. Assoc., 1943, cxxii, 723.
13. Cass, J. W., Jr.: The question of influenza and atypical pneumonia, New England Jr. Med., 1936, ccxiv, 187.
14. Maxfield, J. R., Jr.: Atypical pneumonia with leukopenia, Texas State Jr. Med., 1939, xxxix, 340.
15. Goodrich, B. E., and Bradford, H. A.: The recognition of virus type pneumonia, Am. Jr. Med. Sci., 1942, cciv, 163.
16. Middleton, W. S.: Primary atypical pneumonia, Proc. Cardiff Med. Soc., Session 1942-1943, 1943, pp. 50–57.
17. Reimann, H. A.: The pneumonias, 1938, W. B. Saunders Co., Philadelphia.
18. Pepper, O. H. P., and Farley, D. L.: Practical hematological diagnosis, 1933, W. B. Saunders Co., Philadelphia.

THE USE OF BENZEDRINE SULFATE IN OBESITY *

By FREDERICK K. ALBRECHT, P. A. Surgeon, U. S. Public Health Service,
Baltimore, Maryland

RECENT studies have led to the conclusion that a continuous gain in weight resulting in obesity is caused by eating more than is needed for growth, maintenance and energy requirements. In the normal person, the appetite is satisfied at a point where nourishment is adequate and the weight becomes stabilized. In the obese person the appetite is not satisfied on such a level, and an excessive amount of food is ingested. There is a prevalent belief among some that persons occasionally gain weight even though they do not overeat, and that others do not lose weight when they are underfed. Recent studies [1] lend overwhelming support to the statement that obesity is not caused by lessened expenditure of energy in the basal state. It has been shown by Newburgh that an obese person produces more heat than a normal person of corresponding age, height, and sex. Although both produce the same number of calories per square meter of body surface per unit of time, the obese person has a larger surface area, and therefore the total heat produced by the obese person in the basal state exceeds the total heat produced by the normal person. Strouse, Wang, and Dye [2] have compared the basal metabolic rates of normal persons with those both underweight and overweight. They concluded there was practically no difference. According to Newburgh,[3] the few obese persons whose metabolic rate is low enough to be definitely pathological will be found to be suffering from some disease in which adiposity is a complication or an unrelated accompaniment and not the primary abnormality. Many painstaking studies [4] have demonstrated that the specific dynamic effect is normal in obese persons. For a time it was believed by many endocrinologists that hypofunction of the pituitary, the thyroid, or the gonads offered an adequate explanation of the development of adiposity. Further study has shown this is not the case.[5, 6] No internal secretion is capable of so changing the metabolism that the total amount of fat in the body will increase unless the inflow of calories is greater than the outflow. No one has demonstrated low blood sugars in patients whose chief complaint was obesity. On the other hand, hyperglycemia may commonly be encountered.

The Use of Benzedrine Sulfate as an Adjunct in the Management of Obesity. The problem frequently arises as to how the appetite can be controlled so that a prescribed reducing diet will be adhered to. Lesses and Myerson [17] found that when benzedrine sulfate was administered to various psychotic adult patients, there frequently resulted a decrease in the appetite, a

* Received for publication January 31, 1944.

disappearance of the feeling of fatigue, and a beneficial influence on the state of the mind. With the decrease in appetite there followed voluntary restriction of diet, and weight loss resulted in many patients. On the basis of this work, Kunstadter [7] was induced to treat obesity in children using benzedrine. He administered the drug to 30 obese children between 2½ and 16 years of age who had failed to lose weight on prescribed diets. Many had also received thyroid extract. The drug was given either twice or three times daily, before breakfast and lunch, and after school if a third dose was considered necessary. Many of the children took as much of the drug as usually prescribed for adults without any untoward symptoms. In his series, the majority of patients received a daily dose of from 10 to 30 mg. The average weekly loss of weight of 26 patients who received continuous treatment for over two weeks was 0.831 pounds. There was little or no variation in the basal metabolic rate while under treatment.

Just how benzedrine acts to reduce weight is not entirely clear. In doses of 10 to 30 mg., orally administered, it delays the rate of evacuation of the stomach.[8, 9, 10, 11, 12] The drug apparently relaxes the stomach and increases the tone of the pylorus. Benzedrine has been reported to relax esophageal spasm.[13] Gastric acidity tends to be increased without an increase in volume.[14] The drug has no marked effect upon the small intestine (20–30 mg.) and its effect on the colon is apparently variable, though it has been claimed to be of value in colonic spasm. A study of the available literature reveals considerable difference of opinion concerning the action of benzedrine upon the gastrointestinal tract, and both clinical and animal experimentation has furnished results not entirely consistent. The action of benzedrine upon the small bowel is both uncertain and unpredictable. The cardiovascular response in man to benzedrine is extremely variable. As a rule dosages up to 15 mg. have but little response as to pressor effects if taken orally. Only oral dosages of 30 mg. or more induce any significant increases in tension, and in some cases a paradoxical fall in blood pressure has been reported. It is thus seen that the response to oral administration is unpredictable. Hypertensive patients tend to show a fall in blood pressure when in poor health, whereas hypotensive patients may show an increase in blood pressure.

According to the literature, arrhythmias of different types may occasionally occur including auricular and ventricular extrasystoles, paroxysmal tachycardia, bradycardia, and heart block. The following vascular actions have been reported: flushing, pallor, urticaria and sweating. Patients receiving the drug may complain of dryness of the mouth, palpitation, flatulence, anorexia, nausea, abdominal cramps, diarrhea, or constipation. In the author's experience with more than 400 cases, the principal symptoms reported by the patients are: dryness of the mouth, headache, palpitation, euphoria, coldness of the hands and feet, insomnia if the drug is taken late in the afternoon, and loss of appetite. The inability of benzedrine to ele-

vate the blood sugar has been confirmed by several workers. The rise in the basal metabolic rate following benzedrine administration is negligible, inconstant, and not significant. The few instances in which it has been reported have been attributed to the increased psychomotor activity induced by the drug. Continued administration of the drug has no effect upon the blood picture. The literature contains many references to the value of the drug in helping obese patients adhere to a low calorie diet for reducing purposes.[15, 16, 17, 18, 19] There have been a few reports of a gain in weight following the use of the drug.[20, 21] In cases in which there has been demonstrated a decrease in weight, it has been attributable to increased activity, increased metabolic rate (*this is dubious*), anorexia due to inhibition of gastric tone, and elevation of mood.[22, 23] Bruch [24] suggested that the decrease in appetite and loss of body weight may be due in part to the effect of the drug upon the hypothalamus.

Clinical Results in 300 Cases. In this series of cases reported, 300 patients were studied, 76 males and 224 females. The ages ranged from 21 to 53 years and their weights before treatment was instituted varied from 138 pounds to 310 pounds. The dosage of the drug varied from 10 mg. daily to 30 mg. daily in divided doses. It was never prescribed after 4 p.m. except in a few instances in which the patient was employed at night. The duration of treatment varied, covering periods from two weeks to two months, although in almost all cases the patients were followed for from two to eight months. This follow-up study was greatly facilitated by the fact that many of the patients were hospital personnel such as cooks, maids, office workers and nurses and consequently were seen almost daily in the author's rounds of the hospital. Many of the patients were cooks or others who worked around food and who admitted eating liberally between meals. Many of the office workers, especially the females, admitted almost daily drinking of from one to three coca-colas and an occasional candy bar between meals.

In all cases, treatment was started without any dietary restrictions being imposed, the patient thus eating as his caprice or appetite dictated. When an optimal weight for the individual patient had been reached, the patient was advised to go on a 900 or 1,000 calorie diet. In some cases in which the patient was doing hard manual labor a more liberal diet was allowed. The average weekly weight loss while taking the drug was 4.24 pounds for the males and 3.94 for the females. The greatest individual loss of weight for any one week was 13.5 pounds. The smallest weight loss per week by any one patient was 0.5 pound. This patient admitted drinking large quantities of beer daily. The greatest individual loss of weight was 52 pounds over a period of two months. Twenty-four per cent of the patients noted no apparent loss of weight during the first week of treatment but reported their maximal weekly weight loss as occurring during the second week of treatment. All patients with the exception of one lost weight while taking the drug.

TABLE I

Symptoms Following the Use of Benzedrine

Loss of appetite	88%
Little or no change in appetite	10%
Increased appetite	2%
Psychomotor activity	
Increased	48%
No change	44%
Decreased	8%
Palpitation (all females)	12%
Headache	32%
Xerostomia	56%
Anxiety	14%
Euphoria	22%
Insomnia	4%
Urinary retention	0.33%
Coldness of extremities	2%

In the 12 per cent of cases reporting *palpitation,* it was severe enough in 4 per cent to cause the drug to be discontinued; in the remainder of the patients, it was controlled by the administration of 1 grain of luminal with each dose of the drug. *Anxiety* was present in 14 per cent of the patients. It was not constant, and histories revealed it to have been present to some extent in 8 per cent of cases before taking the drug. *Euphoria* was noted in those who were black coffee drinkers and who followed the morning dose of benzedrine with two or three cups of black coffee. *Insomnia* was directly traceable to the drug being taken late in the afternoon, contrary to medical advice. *Xerostomia* or dryness of the mouth was relieved by chewing gum.

Many patients, especially women, noted no actual weight loss for the first two weeks they were taking benzedrine, yet they were greatly surprised to find that they were able to wear clothes, nurse's uniforms, etc., which they had outgrown years before. In several of these cases, actual measurements revealed a loss of from two to three inches in the waist and hip measurements. Questioning revealed many had been drinking large quantities of water as a result of the induced xerostomia. Chewing gum relieved this immediately, and actual weight loss soon followed. Urinary retention was reported in one case. This patient, an astute observer, noted that when he stopped taking the drug, all signs of retention disappeared only to return on resumption of the drug. The author has been unable to find any other case reported with such symptoms following benzedrine therapy in the literature. This same patient was known to have a moderate arterial hypotension before taking the drug. He felt much better while taking benzedrine, and examination revealed the existence of a moderate pressor response amounting to between 20 and 30 millimeters of mercury systolic pressure, 10 to 14 millimeters of mercury diastolic pressure. Two cases developed a sudden rise in blood pressure which resulted in the drug being discontinued. In one patient it rose from 110 mm. Hg systolic and 80 mm. diastolic to 150 mm. systolic

and 110 mm. diastolic; in another it rose from 160 mm. systolic and 110 mm. diastolic to 200 mm. systolic and 160 mm. diastolic.

One group of 20 patients, all women, was put on the drug for two months and without their knowledge, placebos, having the same size, shape, and taste as benzedrine (Placebo No. 10—Smith, Kline and French) were substituted during the third month of therapy. In 14 of these patients, a loss of weight was seen to continue into the third month, only at a lesser rate than before. They all noted that they had no desire to partake of soft drinks or candy bars between meals. The remaining six patients noted a gradual resumption of their former appetites and they soon fell into their former habit of "nibbling" between meals. A subsequent follow-up after 20 months on the 14 patients mentioned heretofore reveals that 11 of them have been able to curb their appetite and adhere to diets prescribed for them. They have not gained any weight and are not taking any benzedrine.

Additional follow-up studies on 174 patients since 1941, of whom 52 were males and 122 females, reveals that 44 males and only 32 females have been able to stay on their diets and maintain their optimal weight. Many of the female patients bitterly resented having the drug discontinued, and have resumed their former eating habits which has resulted in almost all cases in an increase of weight.

Blood pressures were carefully checked at the beginning of the treatment as well as frequently during the course of therapy and at its discontinuance. Approximately 30 per cent of patients showed an average rise of 8 mm. of mercury systolic pressure. Three per cent of patients showed an average rise of between 10 and 15 mm. of mercury systolic pressure. Twenty-six per cent of patients showed a gradual decrease in blood pressure as they lost weight. Approximately 40 per cent of cases showed little or no change in the blood pressure. It has been observed in the literature,[19, 24] that upon protracted administration of benzedrine, a tolerance to the pressor effect frequently occurs after a few days.

Management of Treatment. Patients are started on 5 mg. of benzedrine sulfate twice daily, the drug to be given one-half to one hour before breakfast and the noon meal. If the patient works at night the dose is adjusted accordingly. In those who eat a very light breakfast and who eat their evening meal fairly early, the drug is given one hour before the noon meal and at 4 p.m. In not a few cases the author has given the drug as late as 6 p.m. without any insomnia resulting. After a few days the dosage can be increased to 10 mg., especially if the patient reports no loss of appetite. It is not uncommon for no loss of weight to be apparent for 12 days following the initiation of therapy. Persistence will usually be rewarded by a rapid loss of weight for a few weeks when it will taper off to a more gradual reduction. Dosage is strictly an individual matter and in many cases 10 mg. has shown an effect comparable to 30 or even 40 mg. daily. Special diets can be started after a few weeks. The author uses those of Newburgh.[8]

Contraindications to Benzedrine Sulfate Therapy. The contraindications to benzedrine sulfate are: (1) a hypersensitivity to epinephrine-like compounds, (2) coronary or other cardiac conditions in which vasoconstrictors are contraindicated, (3) excitability, and (4) insomnia.

Conclusions

Benzedrine sulfate appears to be a valuable adjunct in the management of obesity under the advice and supervision of a physician. Nearly all patients taking the drug lose their propensity for eating between meals and before going to bed. Diets alone, unless they are very low in calories, produce such slow results that the average patient loses heart and does not cooperate in the treatment. Given benzedrine, they see the actual results as weight is lost where most noticeable; their friends are quick to see the result and comment about it which tends to make the patient very happy and enthusiastic in his treatment. They can be put on a diet varying in calories from 450 to 1,500 with an excellent chance that they will stay on it after the drug is discontinued. In some respects the drug is too effective an adjunct to the restricted diet and many patients will seek its continued use as a "crutch." It is apparent that here is an easy and rapid way to lose weight, and, under the guidance and supervision of a physician mindful of the contraindications to benzedrine therapy, relatively free from any ill effects. Obese patients taking the drug lose their uncontrollable desire to eat at various times of the day and are more easily filled at meal time.

Benzedrine should not be considered a panacea, but rather an effective adjunct in the management of selected cases of obesity. The author has seen no case of habituation for the drug either in this series or in his series of 100 cases of seasickness.[25] The weight loss is not permanent; it is transient in the great majority of instances and returns when the drug is discontinued unless the patient remains on his special diet. During the time the drug is being prescribed, however, the patient is able to adjust his abnormal appetite at a new level and may be able to maintain his new weight level for a considerable time after the drug is discontinued.

BIBLIOGRAPHY

1. Grafe, E.: Metabolic diseases and their treatment, 1933, Lea and Febiger, Philadelphia.
2. Strouse, S., Wang, C. C., and Dye, M.: Studies on the metabolism of obesity, Arch. Int. Med., 1924, xxxiv, 275.
3. Newburgh, L. H.: Obesity, Arch. Int. Med., 1943, lxxi, 1033–1096.
4. Strang, J. M., and McClugage, H. B.: The specific dynamic action of food in abnormal states of nutrition, Am. Jr. Med. Sci., 1931, clxxxii, 49.
5. Greene, J. A.: Clinical study of the etiology of obesity, Ann. Int. Med., 1939, xii, 1797.
6. Bruch, H.: Obesity in childhood: 1. Physical growth and development in obese children, Am. Jr. Dis. Child., 1939, lviii, 457.
7. Kunstadter, R. H.: Experience with benzedrine sulfate in the management of obesity in children, Jr. Pediat., 1940, xvii, 490.

8. Ritvo, M.: Drugs as an aid in roentgen examination of the gastrointestinal tract, Am. Jr. Roentgenol., 1936, xxxvi, 868.
9. Van Liere, E. J., and Sleeth, C. K.: The effect of benzedrine sulfate on the emptying time of the stomach, Jr. Pharmacol. and Exper. Therap., 1938, lxii, 111.
10. Rosenberg, D. H., Arens, R. A., Marchs, P., and Nocheles, H.: Benzedrine sulfate: Its limitations in the treatment of the spastic colon and a pharmacologic study of its effect on the gastrointestinal tract, Jr. Am. Med. Assoc., 1938, cx, 1994.
11. Peoples, S. A., and Guttmann, E.: Hypertension produced with benzedrine, Lancet, 1936, i, 1107.
12. Beyer, K. H., and Meek, W. J.: Effect of benzedrine on gastric emptying and intestinal activity, Arch. Int. Med., 1939, lxiii, 752.
13. Schmidt, H. W.: Diffuse spasm of the lower half of the esophagus, Am. Jr. Digest. Dis., 1939, vi, 693.
14. Myerson, A., Rinkel, M., and Dameshek, W.: The anatomic pharmacology of the gastric juice, New England Jr. Med., 1936, ccxv, 1005.
15. Rosenthal, G., and Solomon, H. A.: Benzedrine sulfate in obesity, Endocrinology, 1940, xxvi, 807.
16. Fulton, G., and Humphrey, E. C.: The management of obesity, Kentucky Med. Jr., 1939, xxxvii, 110.
17. Lesses, M. F., and Myerson, A.: Benzedrine sulfate as an aid in the treatment of obesity, New England Jr. Med., 1938, ccviii, 119.
18. Myerson, A., Loman, J., and Dameshek, W.: Physiologic effects of benzedrine and its relationship to other drugs affecting the autonomic nervous system, Am. Jr. Med. Sci., 1936, cxcii.
19. Ulrich, H.: Narcolepsy and its treatment with benzedrine sulfate, New England Jr. Med., 1937, ccxvii, 696.
20. Baker, R. W.: Recognition of orthostatic hypotension, Proc. Staff Meet. Mayo Clin., 1938, xiii, 169.
21. Dub, L. A., and Lurie, L. A.: Use of benzedrine in the depressed phase of the psychotic state, Ohio State Med. Jr., 1939, xxv, 39.
22. Nathanson, M. H.: The central action of benzedrine, Jr. Am. Med. Assoc., 1937, cviii, 579.
23. Beyer, K. H.: The effect of benzedrine sulfate on metabolism and the cardiovascular system in man, Jr. Pharmacol. and Exper. Therap., 1939, lxvi, 318.
24. Bruch, H.: Obesity in childhood, Am. Jr. Dis. Child., 1940, lix, 739.
25. Albrecht, F. K.: Therapeutic evaluation of benzedrine sulfate in the treatment of seasickness: Results in 100 cases, Med. Clin. N. Am., 1943, 1652–1658.

MIGRAINE HEADACHE: SOME CLINICAL OBSERVATIONS ON THE VASCULAR MECHANISM AND ITS CONTROL *

By Miles Atkinson, M.D., F.R.C.S.(Eng.), *New York, N. Y.*

In a previous paper, it was shown that headache possessing all the characteristics of migraine is not uncommonly associated with Menière's syndrome,[1] a fact which was pointed out originally by Menière himself. Sometimes the migraine attacks subside some years before the onset of the Menière attacks, sometimes they are replaced by the Menière attacks, and sometimes the two are present together. It was stated that, in the opinion of the writer, the vascular mechanism producing the two syndromes is identical, and the observations on which this opinion was based were discussed. It was also shown that the treatment directed towards relief of vertigo relieved at the same time the attacks of headache in a large proportion of cases.

In view of these findings, it seemed appropriate to adopt the same procedure of classification and treatment for cases of uncomplicated migraine as had been used for cases of uncomplicated Menière's syndrome in order to determine how far the hypothesis of an identical mechanism was valid, and to what extent identical treatment would prove beneficial. This paper reports the results of such an investigation.

The Material. Twenty-one cases of uncomplicated migraine have been investigated and followed over periods varying from six months as a minimum to two years as a maximum. The criteria adopted for diagnosis have been that paroxysms of unilateral headache associated with nausea or vomiting shall have occurred since adolescence or early adult life, and shall have been severe enough to be incapacitating, at least at times. The association of visual disturbances (nine cases), a hereditary factor (12 cases), or relief by ergotamine tartrate (10 cases) has been regarded as confirmatory evidence in accordance with common current practice. In no case was hypertension present.

The Method of Classification. To make this clear, it is necessary very briefly to recapitulate previous work. Cases of Menière's syndrome, it has been shown, can be divided into two groups by determining their response to an intradermal test for histamine sensitivity, and the validity of this grouping has been established by clinical experiment and therapeutic response.[2, 3] Further, it has been shown that characteristic migraine occurs in both groups and is improved, or in some cases abolished completely, by the treatment appropriate to the group.[1]

* Received for publication November 10, 1943.
Paper read by title at the Clinical Research Meeting of the New York Academy of Medicine, May 27, 1943.

The same procedure was adopted in these 21 cases of uncomplicated migraine. An intradermal test with histamine was performed in the manner and judged by the criteria already described in previous papers. The upshot of this investigation was that no case gave a positive response. This means, if the writer's views about the significance of the test as regards the underlying vascular mechanism are accepted, that no case owned a primary vasodilator mechanism, that every one of the 21 cases of typical uncomplicated migraine owned a primary vasoconstrictor mechanism.

This finding was unexpected. The writer's figures show that, of 22 cases of typical migraine associated with Menière's syndrome, 10 belonged to the primary vasodilator group. If the same proportion of primary vasodilator cases occurred in uncomplicated migraine, at least five out of

TABLE I

21 Cases of Vasospastic Migraine Headache Treated with Nicotinic Acid

Case No.	Date First Seen	Sex	Age of Onset	Family History	Scotoma etc.	Ergot. Tart.	Frequency and Severity		Results			
							Before Tr.	After Tr.	Rel.	Gt. Impt.	Mod. Impt.	Fail.
1	Dec. '42	F	24	+	+	Relief	4/7++++	4/28++			+	
2	Dec. '42	F	15	+	0	Not used	1/28++	0/28	+			
3	Dec. '42	F	10	+	+	No relief	7/7+++	3/7++			+	
4	Nov. '42	M	34	+	+	Relief	1/7+++	1/7++				+
5	Nov. '42	M	35	+	0	Relief	7/7++++	2/7+		+		
6	Nov. '42	M	25	?	0	No relief	2/28++++	1/3 mos. +		+		
7	Oct. '42	F	10	+	+	Not used	3/28+++	3/28+++				+
8	Oct. '42	F	12	0	+	Relief	1/7+++	1/7+++				+
9	Oct. '42	F	34	+	0	No relief	2/28++	0/28	+			
10	Oct. '42	M	18	0	0	Relief	2/28+++	1/28+		+		
11	Sept. '42	F	17	0	0	Relief	1/28++	1/2 mos. +			+	

++++ = very severe. +++ = severe. ++ = moderate. + = mild. *Rel.* = relief. *Impt.* = improvement. *Fail.* = failure.

In the column headed "Frequency and Severity," the numerator of each fraction indicates the average number of attacks in a given interval of time, and the denominator, the length of the interval in days, unless otherwise indicated. The severity is indicated by + marks.

TABLE I—*Continued*

Case No.	Date First Seen	Sex	Age of Onset	Family History	Scotoma etc.	Ergot. Tart.	Frequency and Severity		Results			
							Before Tr.	After Tr.	Rel.	Gt. Impt.	Mod. Impt.	Fail.
12	Sept. '42	M	22	+	+	No relief	3/7++++	1/2 mos. +		+		
13	Sept. '42	F	25	+	0	Relief	2/28++++	1/3 mos. +		+		
14	Sept. '42	F	30	0	+	Relief	3/7+++	3/28+			+	
15	Sept. '42	F	10	0	0	Not used	6/28++++	2/28++			+	
16	June '42	F	19	+	+	Not used	2/28+++	1/3 mos. +		+		
17	June '42	F	21	+	0	Relief	3/7+++	1/28+		+		
18	June '42	F	13	+	0	No relief	1/7+++	1/7+++				+
19	June '42	M	31	0	0	Relief	3/28+++	Occas. +		+		
20	May '41	F	29	0	+	Not used	4/7++++	1/3 mos. +		+		
21	Mar. '41	F	10	0	0	Not used	2/28+++	Occas. +		+		

these 21 cases should have given a positive response to the histamine test. Not one did. The implications of this observation will be discussed later.

Method of Treatment. Since all the cases belonged to the same group, the primary vasoconstrictor, the only form of treatment used was that which had been found satisfactory for the same group in Menière's syndrome, that is to say, nicotinic acid used for its vasodilator action. The reasons prompting the choice of this substance as a suitable vasodilator have been fully discussed elsewhere.[1, 2, 3] There also the method and routine of administration found most satisfactory have been fully described.

Briefly, the routine is to give first an intramuscular injection of 25 to 35 mg. in order to determine by the extent of the flush reaction the individual tolerance of the patient, which can vary within wide limits. Estimating dosage from that, a series of six or eight intravenous injections is given, starting with 20 to 30 mg. and rising by daily increments of 5 mg. to 50 mg. or such lower limit of tolerance as may be determined. A higher dose than 50 mg. is seldom required, and in general the dosage necessary for migraine patients is lower than that for Menière patients. This may be because the vascular tree of the migraine sufferer is more resilient than that of the

Menière patient. Indeed the very fact of having migraine is evidence of a capacity for vasodilation.

After the course of intravenous injections, the patient is taught to give himself intramuscular injections of such a strength (25 to 50 mg.) and at such intervals (daily, three weekly) as experience and the severity of the symptoms indicate.* At the same time tablets (50 to 150 mg. daily) are given. After a period which is determined by the response to treatment, the patient is weaned from injections and kept on a maintenance dose by mouth.

The reason for insisting upon injection therapy in the beginning is that it has been established by experience that many patients who have not responded to nicotinic acid by mouth have responded well when the method of administration has been changed to parenteral. Presumably some people absorb nicotinic acid from the stomach poorly or not at all. In four cases only, none of them very severe, have tablets alone proved sufficient from the beginning.

In addition to medication, a high protein-low carbohydrate diet is recommended, and advice given as to rest and exercise and the beneficial effects on the vasomotor system of alternating warm and cool showers. Smoking is discountenanced and when possible stopped, on the grounds that migraine is a peripheral vascular disorder.

Results. The results are shown in the accompanying table. All patients except three have been seen or have answered a questionnaire within a month of the writing of this report. The three who did not reply have been adjudged on the record of their last visit.

1. *Complete relief* from headaches has been obtained in two cases only, and over periods of six months and four months (headaches averaged previously two a month and one a month respectively, and were only of moderate intensity). This is quite evidently too short a time upon which to base a final estimate. Indeed, it is with some misgiving that this group has been allowed at all, for cure is not a result which can be envisaged in migraine. Because of the unchangeable constitutional background of the condition, the most that can be hoped for is to prevent the mechanism from going into action so frequently and so powerfully and thus to achieve a measure of relief. That this measure can, however, be a considerable one will be seen in considering the next group.

2. *Improvement* has been obtained in 15 cases, and has been classified by the patients themselves as great in 10 cases and moderate in five. Eight suffered frequent very severe and usually incapacitating headaches, the other seven less frequent, less severe and seldom incapacitating headache.

(*a*) *Great improvement* has been obtained in four cases of great severity and in six cases of moderate severity.

Two examples of the very severe group may be briefly mentioned. Case

* The injectable nicotinic acid used in this investigation has been Nicamin (Abbott), generous supplies of which have been provided by Abbott Laboratories, Inc.

20, a woman who had at least one incapacitating headache a week and two or three others less severe but enough to make work a difficulty, now has an occasional mild headache every two to three months. Case 12, a lawyer, had two or three times a month headache of such severity that he would beat his head against the wall, as well as numerous less severe headaches of which he took little account. After nine months of treatment he had no headaches of the severe type and only rarely a headache at all, as long as he took tablets regularly and an occasional injection. Only if, as has occurred once or twice, he commits some gross indiscretion of living, does he have anything in the nature of a severe headache. But, as he says himself, "You can't reasonably expect the stuff to prevent a hangover!"

Of the moderately severe group, case 19 has particular interest. He is a male executive who used to suffer about three fairly severe headaches a month which had been ascribed to allergy, on account of which certain foods (milk, cheese, tomatoes) had been banned. On tablets alone he has been so much improved that he gets no more than an occasional mild headache, in fact claims that he is "cured." Moreover, he finds that now he can take with impunity the foods which formerly he had to avoid.

(*b*) *Moderate improvement* has been effected in four cases of great severity, in one of moderate severity. Two of the four cases of great severity were in women who had daily headaches, whose lives were a misery, and who had come to rely largely on codein for surcease from their sufferings. One had been subjected to many treatments, appropriate and inappropriate. Both are now free of codein, and their headaches, though still frequent, are from the testimony of a daily record kept by themselves, less frequent and less severe, and steadily diminishing.

3. *Failure.* Four cases have been complete failures. No alleviation of symptoms has resulted, though the régime of treatment was faithfully followed. All are in the moderately severe class.

Discussion

The object of this paper is not to add yet another to the long list of migraine "cures," nor to boost nicotinic acid as the final answer to the migraine sufferer's prayers. Its object is rather to discuss the mechanism and classification of migraine, and a rationale of treatment which seems to offer hope.

1. *Mechanism and Classification*

(*a*) Wolff and his co-workers have demonstrated [4] that at least in a portion of cases the basic mechanism of the attack is primary vasospasm which produces the visual disturbances, and that the headache, though the more prominent symptom, is in fact only a manifestation of the secondary or reactionary vasodilation. Substantiation of this view of the mechanism is to be found in the following observation. One of the patients (No. 3)

included in this report started to develop at 7:10 p.m. a visual disturbance which, on the basis of experience, presaged a severe and incapacitating headache. It was possible to give her within 20 minutes of the onset an intravenous injection of 75 mg. of nicotinic acid. The flush reaction even from this large dose was very mild. In five minutes the scotoma began to diminish and in 30 minutes it had disappeared. She went to bed and to sleep, without narcotic, and woke next morning with a slight headache which did not prevent her work as a writer. On other similar occasions she had experienced a much longer period of scotoma and an entirely incapacitating headache on the following day.

(*b*) Other observers maintain that the manifestations of migraine are to be ascribed to an exudative diathesis or allergy, that is to say, in vascular terms, to a primary vasodilator mechanism. There is abundant clinical evidence to support this view of the causation of migraine attacks in at least a proportion of the cases, though the size of that proportion tends to vary with the degree of enthusiasm of the proponent.

Each school of thought maintains its own view to the exclusion of the other—the vasospastic school scoffs at allergy, the allergists at vasospasm. But what if both are right? What if the syndrome known as migraine may be produced by two different mechanisms? What if both these mechanisms are accepted? There is good evidence for each. In that case, there is admitted for the migraine syndrome the identical dual mechanism which the writer has shown to be valid for Menière's syndrome.

These two groups can be differentiated by means of the histamine skin test, at least in patients exhibiting the features of Menière's syndrome.* If the basic mechanism of migraine and of Menière's syndrome is the same, it would be expected that the histamine skin test would be equally effective in both conditions. Yet, as has been said, in this series of 21 cases none showed a positive response to histamine when at least five would have been expected to do so if the proportions of the two groups were the same in the two conditions. Why the discrepancy?

The reason may not be so far to seek. Obviously the numbers involved in this investigation are too small to warrant the drawing of any far-reaching conclusions. Nevertheless, the fact that not one of these 21 cases of uncomplicated migraine belonged to the primary vasodilator group, whereas in cases associated with Menière manifestations almost half of the total (10 out of 22) belonged to this group, suggests that where a primary vasodilator mechanism is at work its effects are more widespread than those of a primary vasoconstrictor mechanism. Whereas vasospasm tends to be a local phenomenon and, therefore, to present symptoms confined to one locality, in the

* It must not be assumed from what has been said that the histamine skin test serves as a satisfactory general test for protein sensitivity, for it does not. Many patients with known allergies, seasonal hay fever for instance, have been tested and found to give a normal response to histamine. The biochemical implications of the test are not as yet clear; its practical value, however, has been proved.

case of migraine to the region of the calcarine fissure, vasodilation on the other hand tends to be a more widespread phenomenon and might, therefore, be expected to affect other areas as well as the calcarine and even other adjacent organs as well as the brain, such as the labyrinth. It is commonly claimed that this is the explanation for the sensory, motor, aphasic and ophthalmoplegic phenomena that are occasionally associated with migraine. It would be of more than passing interest to determine the reaction of such cases to histamine. The opportunity to do so unfortunately has not so far presented itself to the writer.

However that may be, it would seem, as far as the limited observations contained in this paper go, that classical uncomplicated migraine is usually if not always a primary vasospastic phenomenon confined to, or at least mainly manifested in, the calcarine area and followed by a secondary vasodilation of intra- or extradural vessels which produce the headache.

Put another way, the clinical evidence presented here is against the common concept of a primary vasodilator mechanism as exemplified by allergy as a causative factor in uncomplicated migraine. Theoretically, this is what might be expected, since it is difficult to conceive of an exudative process as being sharply localized. As Wilson says "If oedema really causes the visual symptoms it should cause much more at the same time." [7] Perhaps it does.

It looks as if once again similarity of symptoms has led to the grouping under one name of two or more pathologically diverse conditions. Periodic headache is not necessarily migraine, nor is it due to any single cause. It may on the contrary be the result of such diverse conditions as vasospasm, allergy, exudative diathesis or endocrine disturbance. Unfortunately, migraine is too often used loosely to cover all these and others too. Hence, much of the confusion and the multitude of "curses."

2. *The Rationale of Treatment with Nicotinic Acid.* This refers only to the primary vasoconstrictor group, in which the postulated mechanism is a primary vasospasm which produces scotoma, a secondary vasodilation which produces headache. The rationale for the use of nicotinic acid is that, by attacking the primary mechanism with a vasodilator drug, the onset of headache may be prevented, that even in time the mechanism may be overcome. This seems a more rational procedure than to wait for the secondary vasodilation to produce the headache, and then to treat that with vasoconstrictor drugs such as ergotamine tartrate which, whatever their immediate effect upon the headache may be, must and do tend to increase and perpetuate the underlying vasoconstrictor mechanism. It was this same reasoning which actuated Engle and Evanson in their use of potassium thiocyanate,[5] another vasodilator drug.

That the reasoning is sound is indicated by the results obtained both with potassium thiocyanate [5, 6] and with nicotinic acid as reported here. Both are vasodilators and both are at least partially effective in a large proportion of cases. Nicotinic acid has this advantage over potassium thiocyanate, that

it is less potentially dangerous. It has the disadvantage that to obtain satisfactory results, parenteral therapy is usually necessary. Neither, however, has yet been used enough to decide between them. The use of both is empirical in the sense that they attack not the basic cause of the vasospasm, which remains conjectural, but only the effect. Nevertheless, in the present state of knowledge, both drugs would seem to merit more extensive trial.

Summary

1. The results of the treatment of 21 cases of vasospastic migraine with nicotinic acid are described.

2. The mechanism of the migraine syndrome and its possible grouping is discussed, with observations on the results of the histamine skin test in this condition.

3. The rationale for the treatment of migraine with nicotinic acid and with potassium thiocyanate is considered.

BIBLIOGRAPHY

1. Atkinson, M.: Menière's syndrome and migraine; observations on a common causal relationship, Ann. Int. Med., 1943, xviii, 797.
2. Atkinson, M.: Observations on the etiology and treatment of Menière's syndrome, Jr. Am. Med. Assoc., 1941, cxvi, 1753.
3. Atkinson, M.: Diagnosis and treatment of Menière's syndrome, Arch. Otolaryngol., 1943, xxxvii, 40.
4. Wolff, H. G., Cahan, A. M., and Schumacher, G. D.: Studies of migraine: The contrast of vascular mechanism in headache and preheadache phenomena, Proc. Am. Neurol. Assoc., 66th Annual Meeting, June 6–9, 1940.
5. Engle, D. E., and Evanson, C. O.: Effect of potassium thiocyanate on occurrence of migraine, Am. Jr. Med. Sci., 1942, cciv, 625.
6. Hines, E. A., Jr., and Eaton, L. M.: Potassium thiocyanate in the treatment of migraine: a preliminary report, Proc. Staff Meet. Mayo Clinic., 1942, xvi, 254.
7. Wilson, S. A. Kinnier: Neurology, 1941, The Williams & Wilkins Company, Baltimore, vol. II, p. 1587.

SPONTANEOUS MEDIASTINAL EMPHYSEMA *

By Henry Miller, Captain, Medical Corps, A. U. S.

Mediastinal emphysema is not a rare condition and has been recognized clinically for more than a century. McGuire and Bean,[1] in a comprehensive review of the literature prior to 1939, attribute to Laennec the original description of curious grating sounds and bubbling râles during respiration as diagnostic signs of subpleural and interlobar emphysema of the lungs. Hamman [2] points out that even before Laennec physicians had recognized the occurrence of interstitial emphysema of the lung by noticing subcutaneous emphysema about the neck following trauma to the chest and after overdistention of the lungs by violent effort. Pneumomediastinum has been reported secondary to operations on the throat, thyroid, esophagus, lung, and abdomen; following traumatic injury of thorax, rupture of an abdominal viscus and perforation of the esophagus by foreign bodies. It has also been recorded as a complication of artificial pneumothorax, pneumoperitoneum, intubation in children, difficult childbirth, severe exertion and in such diseases as influenzal bronchopneumonia, croup, pertussis, diphtheria, bronchial asthma, and pulmonary tuberculosis.

Müller,[3] in 1888, described certain characteristic physical signs indicative of pneumomediastinum: namely, the presence over the precordium of bubbling crepitations synchronous with the heart beat, the disappearance of cardiac dullness and appearance of subcutaneous emphysema. Since then other investigators [4, 5, 6, 7] have pointed out the diagnostic significance of the peculiar sounds and the mechanism of their production. It was, however, Hamman who first called attention of the medical profession to the clinical picture resulting from the spontaneous occurrence of mediastinal emphysema. As a result of his work there has been a considerable revival of interest in this subject. The literature now contains reports on the clinical features and pathologic physiology which have greatly increased our knowledge of its various aspects and contributed toward its recognition. This recognition in most cases is not difficult when the distinctive sounds heard over the heart and the roentgenographic evidence of air in the mediastinum are present.

Hamman,[8] in 1934, reported in detail three cases of mediastinal emphysema and gained the first widespread recognition for the condition to which his name is often applied. In 1937 he added four additional cases and omitted one of those previously reported in which the condition occurred following irrigation of a maxillary sinus.[2] The same year, Scott [9] reported two cases and called attention to the fact that the pain may simulate that of angina pectoris. In 1939 Hamman [10] added another to his series. Since

* Received for publication January 31, 1944.
From the Medical Service, 333 Station Hospital, A.P.O. 827, United States Army.

then additional cases have been reported by McGuire and Bean,[1] Morey and Sosman,[11] Wolfe,[12] Matthews,[13] Pinckney,[14] Caldwell,[15] Styron,[16] Miller,[17] Murphy and Zeis,[18] Griffin,[19] Lintz,[20] Greene,[7] and Adcock.[21]

One of Scott's [9] cases in which the emphysema came on at the end of a hundred-mile cycle race, one reported by Greene,[7] and another by McGuire and Bean [1] in which the condition came on during childbirth, Wolferth and Wood's [22] patient in whom the symptoms came on during a wrestling match, and Lister's case [23] in which the chest roentgenograms, pleural effusion, and treatment suggested pulmonary tuberculosis should probably not be considered as true cases of spontaneous mediastinal emphysema.

In this paper we wish to add four more to the growing number of cases of spontaneous mediastinal emphysema which have been reported. The particular interest which attaches to our third and fourth cases is derived from the demonstration of an associated spontaneous pneumothorax.

Case Reports

Case 1. A white male, aged 23, was admitted to the hospital on April 4, 1943, complaining of substernal discomfort. He dated the onset of his illness to April 2 when, while lying quietly in bed, he developed a sudden aching pain in the left chest, localized at the level of the third interspace in the midclavicular line. The pain was mild and did not prevent the patient from falling asleep. He attributed it at the time to indigestion, having eaten a hamburger two hours previously. He stated that he had not overexerted himself that day and did not feel tired although he had played two rounds (36 holes) of golf. He felt well the next day, although he again noticed the pain in the left chest that night while lying in bed. About 10 a.m. the next day while walking to the golf course, the pain reappeared with the same intensity, but extended toward the midsternum. At the third golf hole, the pain suddenly became worse and was described as a "heavy gas pain that wanted to be relieved." The pain was worse on deep inspiration, did not radiate toward the shoulders, arms or back and persisted until the patient arrived at the admitting ward.

Physical examination revealed a well-developed young adult who did not appear acutely ill. There was no evidence of dyspnea, orthopnea or cyanosis. Examination of the eyes, ears, nose and throat revealed no abnormalities. Ophthalmoscopic examination revealed normal discs, retina and vessels. The trachea was medial and thyroid gland not palpably enlarged. There was no evidence of subcutaneous emphysema of the neck or chest wall. The lungs were resonant to percussion, the breath sounds vesicular, voice sounds normal, and no râles were heard. The area of cardiac dullness was not enlarged, the outermost border extending 7 cm. to the left of the midsternal line in the fifth interspace. The sounds were distant, but of good quality. The second aortic sound was equal to the second pulmonic sound. No murmurs were heard. Over the entire precordium there were heard loud, crunching, crackling sounds more marked in systole, but also audible in diastole. These sounds were most evident over the sternum and left border of the heart and were not influenced by respiration or position. The patient stated that he could feel "noises in his chest" when the stethoscope was pressed against the precordial region. The heart rate was 80 per minute, and the rhythm was regular; arterial pressure 126 mm. Hg systolic and 78 mm. diastolic. The abdomen was soft and no organs nor masses were felt.

The next day, the patient still had some discomfort substernally but Hamman's sign was markedly diminished and best heard during full inspiration. A few

crepitations were still audible on the fifth hospital day and then disappeared. The patient's course was afebrile.

Laboratory Data. Urine: acid, clear, specific gravity 1.020, no albumin, sugar, cells or casts found. Blood: red blood cells 4,850,000 per cu. mm.; hemoglobin 90 per cent (Newcomer); white blood cells 7,250 with 80 per cent polymorphonuclears and 20 per cent lymphocytes. The blood sedimentation rate (Westergren) was 21 mm. after 45 minutes and 14 mm. on the third hospital day. Three stool specimens were negative for ova, parasites and occult blood. Electrocardiogram: sinus rhythm, rate 74 per minute, auriculoventricular conduction time 0.14 second. The QRS complexes 0.10 second, normal axis deviation. The T waves were high and upright in all leads and lead CF 4 was normal.

Roentgenograms revealed clear lung fields and a normal cardiovascular silhouette. There was no evidence of air in the mediastinum or in the soft tissues of the neck in the P–A or oblique views. There was no roentgenographic evidence of air in the retroperitoneal tissues.

Case 2. A white male, aged 21, was admitted to the hospital on May 8, 1943. He dated the onset of his illness to the previous evening when he drank half a pint of gin. Shortly thereafter he became nauseated and vomited several times. He continued to feel nauseated and vomited all that night and the next morning. He was unable to retain even water and about noon he developed numbness about the lips, hoarseness, sore throat and stiffness of the muscles of both hands. The vomiting gradually subsided and had ceased by the time the patient was admitted to the hospital at 4 p.m. At 8:30 p.m. while sitting quietly in bed, the patient took a drink of water and suddenly developed a sharp pain along the left costal margin and in the epigastrium which extended upward to the level of the second left rib. Within a few minutes it localized in the substernal region and he became conscious of palpitation, fluttering of the heart, and shortness of breath. The pain did not radiate but was worse on deep respiration and swallowing. He was also conscious of pain on both sides of the neck when he turned his head to either side. He felt hot, nervous, and perspired profusely. There was no history of any preceding respiratory infection or cardiovascular symptoms.

Physical examination revealed no abnormalities of the head, eyes, ears, nose or throat. Ophthalmoscopic examination revealed normal discs, retina and vessels. The thyroid gland was not enlarged and the trachea was medial. The soft tissues in both supraclavicular spaces were crepitant with infiltrated air. This was more marked on the left side where the subcutaneous crepitus extended from the anterior border of the left trapezius muscle to the angle of the jaw and down to the left clavicle. In the midline, crepitus was felt from the sternal notch to the level of the thyroid cartilage. On the right side, it was felt for a distance of 2 inches above the right clavicle. The lungs were resonant to percussion, the breath sounds vesicular, voice sounds normal and no râles were heard. There was no evidence of pneumothorax by physical examination. The point of maximum impulse of the heart could not be felt and the area of cardiac dullness was not determined, the dullness being replaced by a markedly hyperresonant percussion note. The sounds were distant. The rate was 88 per minute and rhythm was regular. No murmur was heard. Over the entire precordium and from the right mid-sternal line to the left anterior axillary line, peculiar, loud, crunching, crackling sounds were heard. They were systolic in time and were loudest during full inspiration. The arterial pressure was 132 mm. Hg systolic and 80 mm. diastolic. The abdomen was soft, and no organs or masses were felt. There was no costovertebral angle tenderness.

The next day, the patient still complained of discomfort under the sternum and pain along both sides of the neck especially on chewing movements of the jaw and on swallowing. The subcutaneous emphysema disappeared in 72 hours and Hamman's

sign in six days. The temperature on entry was 99.2° F., 98.8° for the first three days, then remained normal.

Laboratory Data. Urine: acid, clear, specific gravity 1.024, no albumin, sugar, cells or casts found. Blood: erythrocytes 5,050,000 per cu. mm.; hemoglobin 100 per cent (Newcomer): white blood cells 9,200 with 70 per cent polymorphonuclears, 26 per cent lymphocytes and 4 per cent eosinophiles. The blood sedimentation rate (Westergren) was 8 mm. after 45 minutes. Three stool specimens were negative for ova and parasites. Electrocardiogram: sinus rhythm, rate 83 per minute, auriculoventricular conduction time 0.14 second. The QRS complex 0.06 second, slight left axis shift. The T waves were high and upright in all leads and lead CF 4 was normal.

Roentgenograms revealed fairly extensive emphysema in the soft tissues on both sides of the neck, extending into the superior mediastinum (figure 1). In the P–A and oblique views, no pneumomediastinum could be demonstrated.

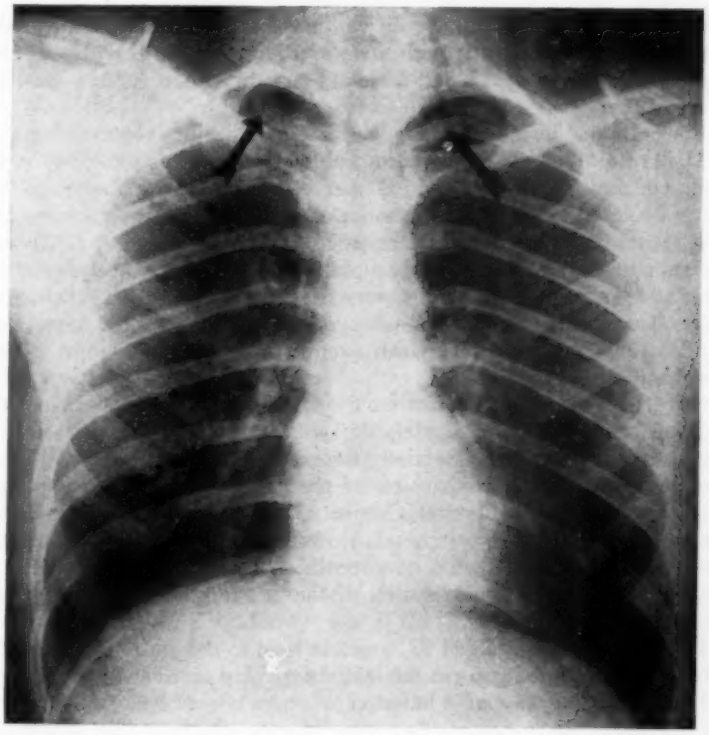


FIG. 1. Roentgenogram of the chest. The arrows indicate the air in the soft tissues of the neck extending from the superior mediastinum.

Case 3. A white Army officer, aged 28, was admitted to the hospital on October 14, 1940, complaining of pain in the left chest. On October 12 he suddenly developed a pain under the left scapula which rapidly spread to involve the left shoulder and entire left side of the chest. The pain was sharp, stabbing in character and was accentuated by movements of the body, deep inspiration and spasmodic spells of severe, hacking, non-productive cough. Associated with this pain he developed the sensation of a heavy weight within the chest and shortness of breath when he turned on his left side. He stated that since July he had suffered five moderately severe

upper respiratory infections. About July 20 and again in the latter part of August, he had developed pain in his right chest similar to that which he now had on the left side. Both of these subsided within a few hours. There were no symptoms referable to the gastrointestinal or genitourinary systems and nothing in his familial, past or systemic history to suggest a diagnosis of tuberculosis.

Physical examination revealed a well-developed adult who did not appear acutely ill. The pharynx was moderately injected. Chest expansion was slightly limited on the left side, the percussion note was hyperresonant and the breath sounds and voice sounds were diminished on the left side. No râles were heard. By percussion, the heart was normal in size and position. The heart sounds were distant, the rate 68 per minute, the rhythm regular, and no murmurs were heard. Over the lower left border of the sternum, there were audible "peculiar scratching, crackling sounds" in both systole and diastole, loudest in full inspiration. The arterial pressure was 120 mm. Hg systolic and 68 mm. diastolic. The abdomen was soft and no organs or masses were felt.

The patient's course in the hospital was afebrile. The pain disappeared within 24 hours and except for a slight cough, he was asymptomatic thereafter. Hamman's sign was audible on October 17 and 19 and then disappeared. He was discharged November 9, 1940.

Laboratory Data. Urine: amber, clear, acid, specific gravity varied between 1.012 and 1.020; no albumin, sugar, casts or cells were noted. Blood: erythrocytes, 4,180,000 per cu. mm. and hemoglobin 80 per cent. On entry, the white blood cells were 16,040 with 89 per cent polymorphonuclears, 1 per cent eosinophiles and 10 per cent lymphocytes. On October 16 it was 9,320 and on October 17, 5,920 with 72 per cent polymorphonuclears, 1 per cent basophiles and 27 per cent lymphocytes. The Wassermann and Kahn blood reactions were negative. Several smears were negative for malaria. The blood non-protein nitrogen was 35.1 mg. per cent and fasting blood sugar 96.0 mg. per cent. Thirteen examinations of the sputum were negative for tubercle bacilli.

On October 16 radiographic examination revealed a partial pneumothorax on the left side. There was approximately 35 per cent collapse of the left lung. The heart and lungs were otherwise essentially normal. On October 24, roentgenographic examination revealed partial reëxpansion of the left lung with approximately 20 per cent collapse remaining. A film on October 31 revealed complete reëxpansion of the left lower lobe with slight compression of the left upper lobe by pneumothorax. There was no evidence of fluid and no parenchymal abnormalities noted. A film on October 31 revealed complete reëxpansion of the left lung. Another film on November 20 was normal.

Case 4. A white soldier, aged 23, was admitted to the station hospital on December 13, 1943, complaining of pain in the left chest. He dated the onset of his present illness to 11 a.m. on the day of admission when, while walking down the road, he suddenly developed a sharp constricting type of pain over the left breast. The pain rapidly became worse over a period of 10 minutes and then rapidly subsided to be replaced by an aching pain just below the costal margin and in the supraclavicular region of the left chest. This pain was accentuated by any attempt to take a deep breath. A few minutes after the onset of the pain, he became short of breath. This was described as an inability to take a deep breath and lasted approximately 20 minutes. Both the pain and dyspnea were increased during the slight exertion of getting into the ambulance, but disappeared shortly after he resumed a recumbent position and did not recur. On December 10, the patient had developed a chest cold manifested by a slight, hacking, non-productive cough without any associated chest pain. He still had a slight cough at the time of entry. There was no history of familial tuberculosis, no personal history of hemoptysis, night sweats, fever or chill and he had gained approximately 10 pounds in weight during the past year.

Physical examination revealed a tall, fairly well-developed young male in no respiratory distress. The skin was clear and tanned. There were no abnormalities of the head, eyes, ears, nose or throat. The trachea was slightly deviated to the right side. Respiratory excursions of the left side of the chest were moderately diminished. Tactile fremitus was diminished over the entire left chest and percussion note was hyperresonant with extension of the hyperresonant note to the lowest position of the pleural space. The breath sounds and vocal fremitus were absent over the involved lung anteriorly and posteriorly. No râles were heard. The area of cardiac dullness was replaced by a hyperresonant percussion note and the right border could not be detected by percussion. The sounds were somewhat distant. The second pulmonic sound was louder than the second aortic sound. The rhythm was regular, the rate was 72 per minute and no murmurs or adventitious sounds were heard. The arterial pressure was 136 mm. Hg systolic and 80 mm. diastolic. The abdomen was soft and no organs nor masses were felt.

On December 19 the patient reported that he heard "peculiar sounds" in his left chest, and on December 21 the hospital radiologist, Captain Jerome L. Marks, reported the presence of air in the mediastinum. However, careful examination failed to reveal any change in the physical signs until the morning of December 22, when the typical crackling, crunching sounds were heard over the lower one-third of the sternum. These sounds were high pitched, present in systole and diastole, and were best heard with the patient in the upright position and in full expiration. The patient's course in the hospital was afebrile and asymptomatic. Hamman's sign persisted until January 6, but varied greatly in intensity and quality on different days.

Laboratory Data. Urine: acid, clear, specific gravity 1.012, no albumin, sugar and an occasional white blood cell per high power field. Blood: erythrocytes 5,150,000 per cu. mm.; hemoglobin 95 per cent (Newcomer); white blood cells 9,700 with 78 per cent polymorphonuclears and 22 per cent lymphocytes. The blood sedimentation rate (Westergren) was 5 mm. after 60 minutes.

An electrocardiogram on December 14, revealed a sinus mechanism with a rate of 64 per minute and an A–V conduction time of 0.18 second. The QRS complexes measured 0.08 second and the T waves were upright and normal in all leads.

Radiographic examination of the chest on December 13 revealed the presence of a left pneumothorax with approximately 50 per cent collapse of both lobes. There was a slight shift of the mediastinal structures to the right. On December 20 (figure 2) radiographic examination of the chest revealed approximately 35 per cent pneumothorax in the left thoracic cavity. There was still evident a slight shift of the mediastinal structures to the opposite side. There was also present a small collection of air between the pleura of the left lung and the cardiac silhouette in the region of the arc of the pulmonary artery and left auricle, indicative of mediastinal emphysema. On January 2 the left lung had completely reëxpanded and there was no evidence of any parenchymal lesion.

Pathologic Physiology. The probable explanation of the genesis of spontaneous mediastinal emphysema is contained in the series of experiments of Macklin.[24] By artificially increasing the intrapulmonary pressure in a lobe of the lung of cats and other animals, he was able to demonstrate that the air enters the perivascular sheaths of the finer branches of the pulmonary vessels, presumably through the numerous minute ruptures in the walls of the alveoli. As the increased intrapulmonary pressure continues, the small bubbles of air coalesce into large ones as they move toward the root of the lung through the artificially produced channels in the vascular sheaths. At the root of the lung, the air bubbles may merge into large blebs which can

impede the pulmonary circulation. Further leakage causes these blebs to break through into the mediastinum. At times, the air in the perivascular sheaths may extend into the adjoining connective tissue and dissect a pathway toward the pleura where it forms a subpleural bleb, particularly in the region of the root of the lung. Rupture of this bleb may occasionally produce a pneumothorax.

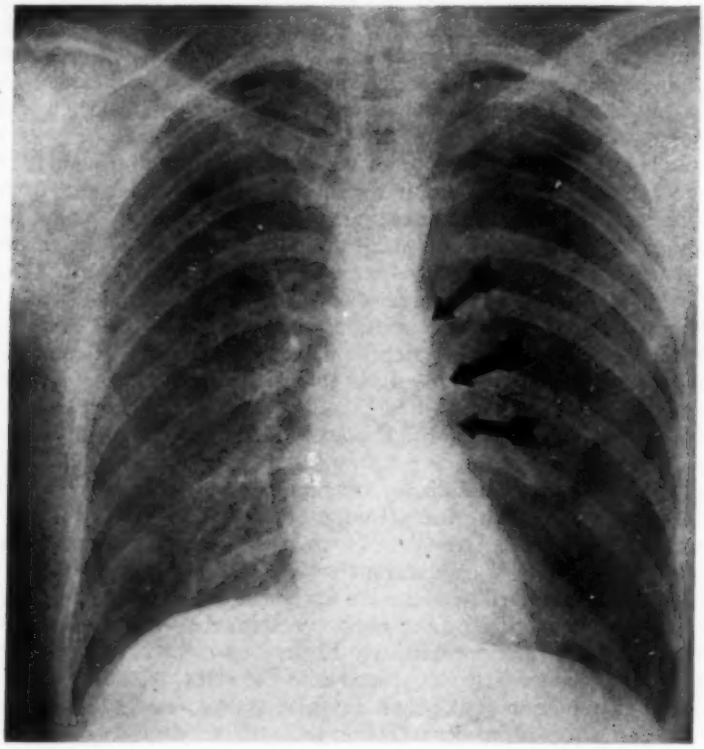


FIG. 2. Roentgenogram of the chest showing pneumothorax on the left side and an area of lessened density due to mediastinal emphysema.

The paths of extension of air in the mediastinum have been made the subject of special study by Ballon and Francis [25] and more recently by Macklin.[24] The air tends to follow with predilection the fascial planes, particularly the sheaths surrounding blood vessels. It may spread upward into the root of the neck, the face, axilla, anterior chest wall and arms. It is possible for it to dissect up along the sides of the trachea to the floor of the mouth extending under the base of the tongue which becomes elevated. It may extend forward between the parietal pleura and pericardium to appear as blebs overlying the heart, laterally into the opposite lung and downward into the retroperitoneal space where it may outline the kidneys, ureters and renal vessels.

Diagnosis. Clinically, the spontaneous type of mediastinal emphysema described by Hamman is characterized by the sudden development of pain in the chest in the absence of any antecedent trauma or unusual effort. The location and severity of the pain vary a great deal in different cases, depending largely on the degree of distention of the mediastinal tissues. It is usually described as severe, sharp, and stabbing although it may be mild, dull and aching in character. Occasionally there may be no associated pain.[21] Not infrequently pain in the left chest precedes the precordial pain. This has been attributed to interference with the blood flow in the pulmonary vessels of the lung by the pressure of air bubbles in the perivascular sheaths. The pain may radiate to the upper midback, shoulders, neck and occasionally down the left arm as it does in angina pectoris. There is also at times a pressure sensation under the sternum, and the patient may complain of pain on deep breathing, on swallowing, or on movement of the head. The duration of the pain is very variable, lasting from several hours to several days. Its character and radiation have at times led to the erroneous diagnosis of coronary occlusion. Macklin suggests that this radiation is due to pressure on the coronary vessels through both layers of the pericardium whereas Scott believes it is due to pressure of the mediastinal air on the aorta and surrounding tissues.

The patients frequently prefer certain positions in which the pain is decreased. Dyspnea, cyanosis, and orthopnea may occur but are not characteristic of the spontaneous cases of mediastinal emphysema. In uncomplicated cases there is no clinical evidence of serious constitutional disturbance. Occasionally the temperature may be elevated for the first few days, but the blood pressure, white blood counts, sedimentation rate and electrocardiogram are usually within normal limits.

The demonstration of air in the subcutaneous tissues of the neck and anterior chest wall by palpation is diagnostic. The area of cardiac dullness is often diminished or completely obliterated, being replaced by a hyperresonant percussion note.

The pathognomonic sign of mediastinal emphysema is the peculiar sound heard over the pericardium on stethoscopy and sometimes even with the unaided ear. It has been variously described as crunching, crackling, popping, clicking, tapping, snapping, crepitant, etc., and is synchronous with the heart beat. This has been termed Hamman's sign and attributed by him to the action of the heart on air between the anterior parietal pericardium and the chest wall. Macklin's experimental studies corroborated this clinical impression. When he removed the sternum in his experimental animals, a froth of bubbles was found over the parietal pericardium. The sound has been likened to the "squeak of a leather saddle," "rubbing two inflated balloons together," "crackling of cellophane," etc. Changes in position and phase of respiration may cause a change in the intensity of the noises. It is usually heard during systole but may also be heard during diastole.

Pneumothorax was present in some of the reported cases of mediastinal emphysema. It is usually small and not detected except by roentgenograms of the chest. Pneumoretroperitoneum is very common in experimental animals and has been reported following traumatic emphysema in man. In Adcock's case,[21] the retroperitoneal emphysema was quite extensive, and the air could be felt in the pararectal tissues by digital examination. The condition was also suspected in one of Griffin's cases in whom upper abdominal pain, an area of tympany in the left upper abdomen and tenderness over this area were present.

Roentgenographic demonstration of air in the mediastinum is diagnostic. In the anteroposterior view only the outlying pockets of air may be seen, so that lateral and oblique views should also be taken. In the anteroposterior view, a sharp line running parallel to the outer wall of the mediastinum in the presence of a pneumothorax may be detected. In the lateral and oblique views, air may be visible between the heart and the anterior chest wall or in the posterior mediastinum. In rare cases when the air does not extend forward around the heart, Hamman's sign may be absent and the roentgenographic evidence of air in the mediastinum may be decisive. Air may also be detected in the subcutaneous tissues of the neck and in the retroperitoneum.

In the differential diagnosis, coronary occlusion, pericarditis, dissecting aneurysm and pulmonary embolus must be considered. These can usually be differentiated by physical examination, roentgenographic examination of the chest and electrocardiography.

Treatment is symptomatic and the prognosis, in general, is excellent. Resorption of air from the mediastinum is rapid when the point of entry is closed. It is possible that in the future some of the complications occurring in experimental animals may develop in man. If a large amount of air should escape from the lung, the pressure in the mediastinum could produce circulatory embarrassment and necessitate active treatment such as the induction of an artificial pneumothorax or incision to allow the air to escape externally. Infection from the alveoli along false channels may produce pneumonia and even mediastinitis.

Discussion

There is increasing evidence that the syndrome under discussion occurs more frequently than the number of reported cases indicate. The cases presented conform closely to the previously established criteria for diagnosis. The most constant feature is the peculiar and distinctive sound heard over the heart synchronous with its contractions. In the majority of reported cases, no definite evidence of pulmonary disease has been demonstrated. Macklin has suggested that small areas of atelectasis, by causing over-distention of the surrounding alveoli, may lead to escape of air into the perivascular sheaths. No such areas of atelectasis could be demonstrated in the roent-

genograms of any of the four cases. However, the author has recently seen a case in which this was undoubtedly the mechanism of production of mediastinal emphysema. This patient was seen after he had recovered from his acute illness.

Case 5. A white male, aged 21, was admitted on March 22, 1943, with the diagnosis of chronic, bilateral, follicular tonsillitis. On March 23, 1943, a bilateral tonsillectomy was performed under 1 per cent novocaine anesthesia. At 1:30 a.m. on March 24, the patient was seen by a physician because of severe precordial pain, cyanosis, and cough productive of frothy, brownish-red sputum. On examination, the patient was dyspneic, cyanotic and in marked distress. The trachea was deviated to the right side, dullness to percussion and absent breath sounds were elicited over

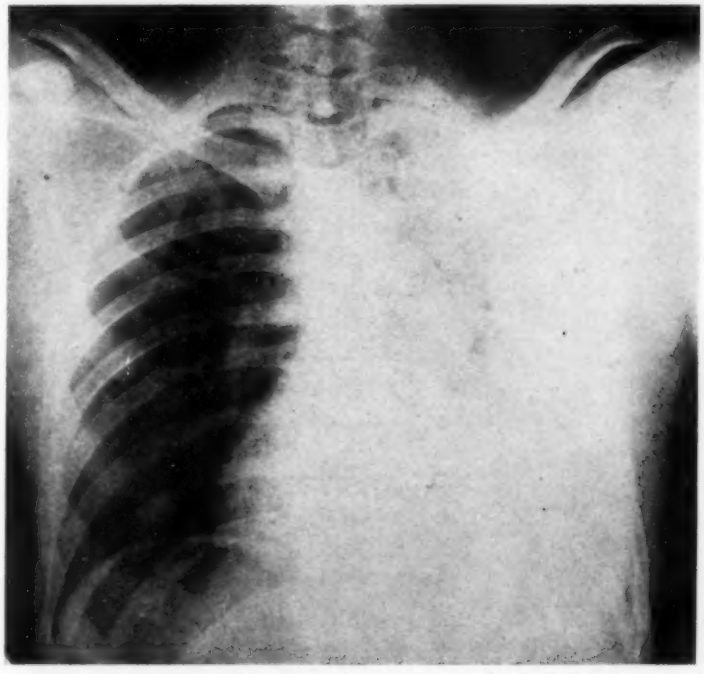


FIG. 3A. Roentgenogram of the chest taken March 24 revealing massive atelectasis of the right lung with shift of the mediastinal contents to the affected side.

the right middle and lower lobe. The area of cardiac dullness was displaced to the right and the basal heart sounds were best heard below the right clavicle. Over the third rib and interspace parasternally there was audible a peculiar sound described by various observers as a "clicking sound suggestive of a pericardial rub," "a high-pitched pleuro-pericardial friction rub," and a "pericardial friction rub." The temperature rose to 102° F. The leukocyte count was 25,600 with 85 per cent polymorphonuclears and 15 per cent lymphocytes. A roentgenogram of the chest taken March 24 (figure 3A) revealed marked retraction of the trachea, mediastinum and heart toward the right side. The entire right lung was atelectatic and the right diaphragmatic shadow obliterated. The diagnosis was "massive atelectasis of the right lung." An electrocardiogram revealed right axis shift, and flattening of the T waves in all leads.

On March 24, under 5 per cent novocaine spray anesthesia, a rubber catheter was inserted in the trachea and a large amount of mucopurulent material was aspirated by suction with marked clinical improvement. The next day, the procedure was repeated and some more mucopurulent material was aspirated from the right main bronchus. On March 25, the roentgenogram of the chest (figure 3B) revealed that the heart and mediastinum had returned to their normal position and the right lung was almost completely aerated. Incidentally, the presence of subcutaneous emphysema on both sides of the neck was reported. At this time, the air in the subcutaneous tissues of the neck was detected clinically and a note was made that the patient complained of severe pain in the neck. The subcutaneous emphysema slowly disappeared

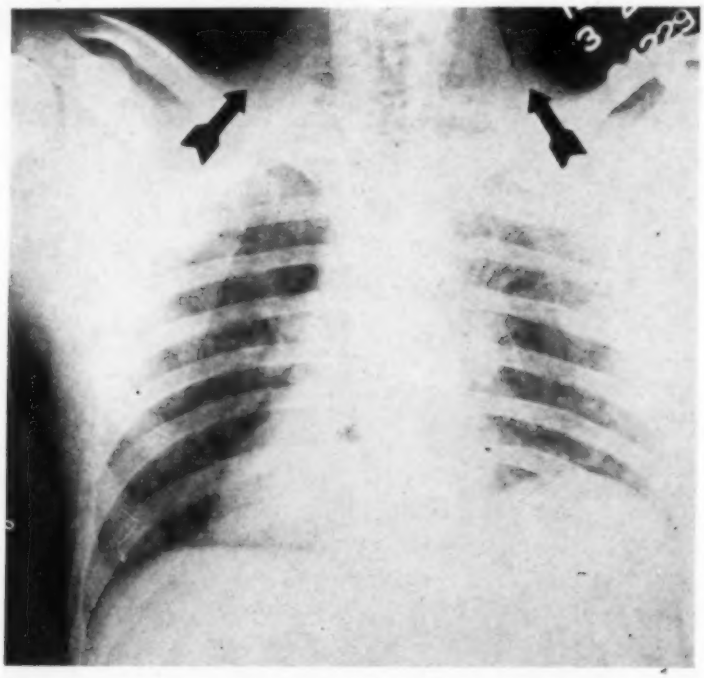


FIG. 3B. Roentgenogram on March 25 shows reëxpansion of the right lung with the presence of subcutaneous emphysema on both sides of the neck.

and the patient improved rapidly. Roentgenograms of the chest on March 29 and April 4 were normal, and an electrocardiogram on April 1 was also within normal limits.

The findings in this case can be explained by overdistention of the left lung following postoperative massive atelectasis of the right lung. The alveolar ectasia in the left lung permitted the air to escape into the perivascular sheaths and lead to mediastinal and subcutaneous emphysema. The careful pathologic study by Fisher and Macklin [26] of a child with foreign body atelectasis of the lung supports this theory of the mechanism of formation of mediastinal emphysema.

Although it is now generally appreciated that spontaneous pneumothorax

may occur in the absence of any preëxisting pulmonary disease, the etiology of the condition is still obscure. One of the most commonly accepted theories is that of rupture of emphysematous blebs occurring on the surface of the pleura. In his experimental animals, Macklin noted the penetration of air from the perivascular sheaths into the connective tissue and eventually to the pleura where it formed a subpleural bleb. More commonly however, pneumothorax was due to the escape of air from the mediastinum. He was able to demonstrate that the air reaches the pleural cavity via a tear in the mediastinal wall. He was able to force air from the mediastinum into the pleural cavity, but by increasing the intrapleural pressure after induction of a pneumothorax, he was never able to get air to penetrate the mediastinum.

Hamman suggests that his mechanism—rupture of air from the mediastinum into the pleural cavity—is a better explanation for the development of some cases of benign spontaneous pneumothorax than the theory of a ruptured subpleural bleb. Physiologically, the pneumothorax may be beneficial. By collapsing the lung, it stops further leakage of air into the vascular sheaths, relieves the pressure on the mediastinal structures and frees the circulation in the lungs.

It is of interest that the pneumothoraces present in cases 3 and 4 were large enough to be detected on physical examination. Usually they are detected only by radiographic examination of the chest. As in previously described cases, the pneumothoraces were on the left side. Hamman predicts that in the future, they will probably be found on the right side as well.

In each case the diagnosis was made by detection of the typical sounds over the heart. As has been pointed out previously, these sounds may show great variation in intensity and quality during the course of the condition. They may be detected some time after the appearance of spontaneous pneumothorax and may last for several weeks.

Summary

The literature regarding the clinical picture and pathologic physiology of spontaneous mediastinal emphysema has been reviewed. Four additional cases illustrating the essential clinical picture of the syndrome are reported. In two of these, an associated spontaneous pneumothorax was demonstrated. Another case report of mediastinal and subcutaneous emphysema following atelectasis of the lung lends further support to Macklin's theory as to the underlying mechanism of spontaneous mediastinal emphysema.

BIBLIOGRAPHY

1. McGuire, J., and Bean, W. B.: Spontaneous interstitial emphysema of the lungs, Am. Jr. Med. Sci., 1939, excvii, 502–509.
2. Hamman, L.: Spontaneous interstitial emphysema of the lungs, Trans. Assoc. Am. Phys., 1937, lii, 311–319.
3. Müller, F.: Ueber Emphysem des Mediastinum, Berl. klin. Wchnschr., 1888, xxv, 205–208.

4. Rees, W. A., and Hughes, G. S.: Wounds of the chest as seen at an advanced operating center, Lancet, 1918, i, 55–59.
5. Smith, S. M. S.: Pericardial knock, Brit. Med. Jr., 1918, i, 78.
6. Munden, W. P. H.: Pericardial knock, Brit. Med. Jr., 1918, i, 174.
7. Greene, J. A.: Unusual sounds emanating from the chest, Arch. Int. Med., 1943, lxxi, 410–414.
8. Hamman, L.: Remarks on the diagnosis of coronary occlusion, Ann. Int. Med., 1934, viii, 417–431.
9. Scott, A. M.: The significance of the anginal syndrome in acute spontaneous pneumomediastinum, Lancet, 1937, i, 1327–1330.
10. Hamman, L.: Spontaneous mediastinal emphysema, Bull. Johns Hopkins Hosp., 1939, lxiv, 1–21.
11. Morey, J. B., and Sosman, J. C.: Spontaneous mediastinal emphysema, Radiology, 1939, xxxii, 19–22.
12. Wolfe, B. P.: Spontaneous interstitial emphysema of the lungs, Ann. Int. Med., 1940, xiii, 1250–1252.
13. Matthews, E. P.: Spontaneous mediastinal emphysema, New Orleans Med. and Surg. Jr., 1941, xciii, 523–524.
14. Pinckney, M. M.: Mediastinal emphysema and idiopathic spontaneous pneumothorax, Virginia Med. Monthly, 1941, lxviii, 315–319.
15. Caldwell, H. W.: Spontaneous mediastinal emphysema, Jr. Am. Med. Assoc., 1941, cxvi, 301–302.
16. Styron, C. W.: Spontaneous mediastinal emphysema, New England Jr. Med., 1941, ccxxv, 908–909.
17. Miller, U.: Spontaneous interstitial emphysema of the lungs, Ohio State Med. Jr., 1941, xxxvii, 1056–1059.
18. Murphy, J. P., and Zeis, L. B.: Spontaneous interstitial mediastinal emphysema, Jr. Missouri Med. Assoc., 1942, xxxix, 5–7.
19. Griffin, R. J.: Spontaneous pneumothorax, Kentucky Med. Jr., 1941, xxxix, 284–288. A diagnostic sign of interstitial emphysema of the mediastinum, Ann. Int. Med., 1942, xvii, 295–297.
20. Lintz, R. M.: Spontaneous mediastinal emphysema, Arch. Int. Med., 1943, lxxi, 256–261.
21. Adcock, J. D.: Spontaneous interstitial emphysema of the lung with mediastinal, retroperitoneal and subcutaneous emphysema, Arch. Int. Med., 1943, lxxi, 650–657.
22. Wolferth, C. C., and Wood, F. C.: Angina pectoris, Med. Clin. North Am., 1930, xiii, 947–967.
23. Lister, W. A.: A case of pericardial knock associated with spontaneous pneumothorax, Lancet, 1928, i, 1225–1226.
24. Macklin, C. C.: Pneumothorax with massive collapse from experimental local overinflation of the lung substance, Canad. Med. Assoc. Jr., 1937, xxxvi, 414–420. Transport of air along sheaths of pulmonic blood vessels from alveoli to mediastinum: clinical implication, Arch. Int. Med., 1939, lxiv, 913–926. Impediment to circulation occasioned by pulmonic interstitial emphysema and pneumomediastinum, Jr. Mich. Med. Soc., 1940, xxxix, 756–759.
25. Ballon, H. C., and Francis, B. C.: Consequences of variations in mediastinal pressure: mediastinal and subcutaneous emphysema, Arch. Surg., 1929, xix, 1627–1659.
26. Fisher, J. H., and Macklin, C. C.: Pulmonic interstitial and mediastinal emphysema: report of a fatal case in which the emphysema occurred in a child as a result of the aspiration of peanut fragments, Am. Jr. Dis. Child., 1940, lx, 102–115.

SPONTANEOUS PNEUMOTHORAX: A REPORT OF THREE UNUSUAL CASES*

By ALFRED GOLDMAN, M.D., F.A.C.P., and HAROLD ROTH, M.D.,
St. Louis, Missouri

RECENTLY there were encountered on the Ward Service of the Barnes Hospital three patients with spontaneous pneumothorax, each of whom exhibited complications which seemed of sufficient interest to us to warrant reporting. The first patient was a 51 year old man with congenital cystic disease of the lung. Treatment in this case proved to be of particular interest. The second patient suffered a spontaneous pneumothorax with complete atelectasis of the left upper lobe. This complication has been reported only once before. The third patient had a spontaneous hemopneumothorax with recovery followed two months later by a spontaneous pneumothorax. It has generally been assumed that the occurrence of spontaneous pneumothorax after hemopneumothorax is impossible because of the formation of adhesions. Although the cases present unrelated aspects of spontaneous pneumothorax, it was decided to group them together for the sake of brevity.

CASE REPORTS

Case 1. M. B., a 51 year old Polish barber, entered Barnes Hospital August 1, 1942. His past history was significant in that between the ages of 26 and 28 he worked in a copper mine tunnelling through quartz. At this time he began to cough up sputum flecked with black particles. At the age of 32 he stated that he was found to have syphilis for which he received apparently adequate treatment. The patient then felt well until the age of 41, when he developed attacks of shortness of breath. These would last up to two hours and come as often as every two weeks to two months. At the age of 45, he had an attack of dyspnea lasting three weeks and associated with severe pain in the right side of the chest.

The patient's present attack of dyspnea began two weeks prior to his admission and was the most severe attack that he had experienced. He stated that he had a moderate cough, productive of a tablespoonful of gray, black flecked sputum a day, and a dull pain in the right chest, for the past six months.

Physical Examination. Temperature 38.4° C. Pulse 100. Respirations 28. Blood pressure 124 mm. Hg systolic and 94 mm. diastolic. The patient was markedly orthopneic, dyspneic, and moderately cyanotic. The important physical findings were limited to the chest. The trachea was deviated to the left. There was slight lag of the right side of the chest. Percussion note over the right was tympanitic while the breath sounds, voice sounds, and tactile fremitus were markedly diminished. The left lung was essentially negative. The heart was displaced to the left.

Laboratory Findings. Blood count: red blood cells 5,300,000, hemoglobin 13.4 grams; white blood cells 9,250, differential count normal. Urine negative. Kahn reaction negative. Five sputa negative for tubercle bacilli. Vital capacity 1,600 c.c.

* Received for publication April 16, 1943.
From the Department of Internal Medicine, Washington University School of Medicine and the Barnes Hospital, St. Louis, Missouri.

Roentgenographic examination of the chest, August 8, 1942, showed a large pneumothorax pocket in the right chest with almost complete collapse of the lower portion of the right lung (figure 1). The apical portion of the right lung was held up by adhesions. The upper portion of the right lung field revealed numerous areas of decreased density having very thin walls about them. Several of these areas were also noted in the upper portion of the left lung field. Lipiodol bronchograms did not show any filling of the cystic areas.

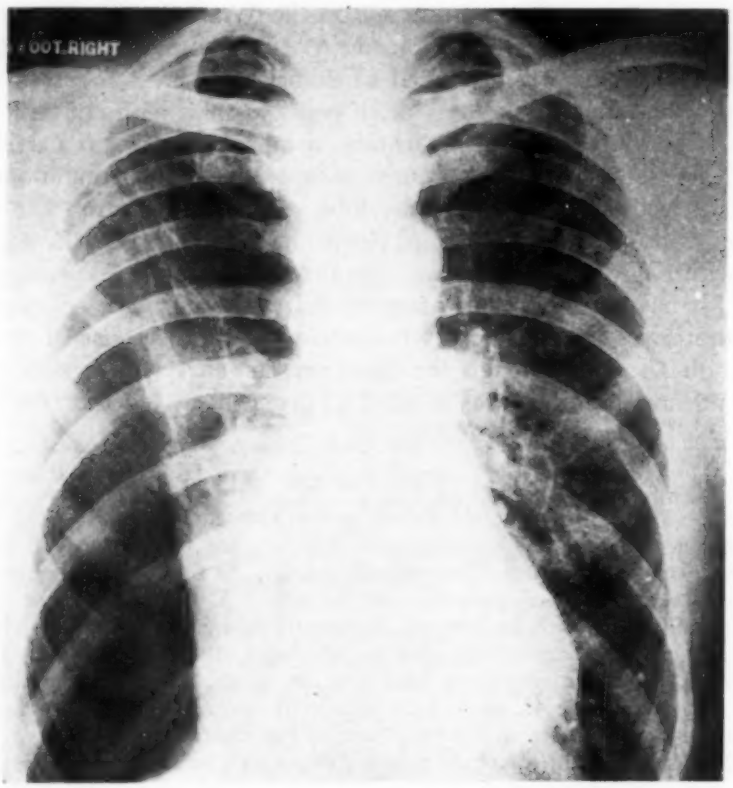


FIG. 1. (Case 1, 8/3/42) Spontaneous pneumothorax associated with cystic disease of the lung. Note rarefied areas in both apices.

Course in the Hospital. The patient's temperature dropped to normal on his first hospital day. Because of the severe dyspnea, 250 c.c. of air were removed from the right chest on August 4, 1942. The initial pressure reading was minus 5 plus 5; the final pressure reading was minus 10 plus 3. There was no immediate relief. From August 4 to August 18, there was no evidence of reëxpansion. On August 18, 1,000 c.c. of air were aspirated with a final pressure reading of minus 15, minus 5, and at the same time 15 c.c. of the patient's whole blood were injected into the right pleural space. On August 11, the patient's vital capacity was 3,100 c.c. and his pneumothorax was no longer evident.

He was discharged on August 22, 1942, completely relieved of his chest pain and dyspnea (figure 2).

Comment. It is difficult to distinguish between congenital cystic and acquired cystic disease of the lung. In this case dyspnea was first noted at the age of 41, the patient apparently being free of all symptoms up to that time. Although this would suggest an acquired origin, it has been pointed out many times that patients with congenital cystic disease of the lung may have no symptoms until late in life. In a recent review [1] of 374 cases of cystic disease of the lung, it was stated that 207 of the cases were first noted

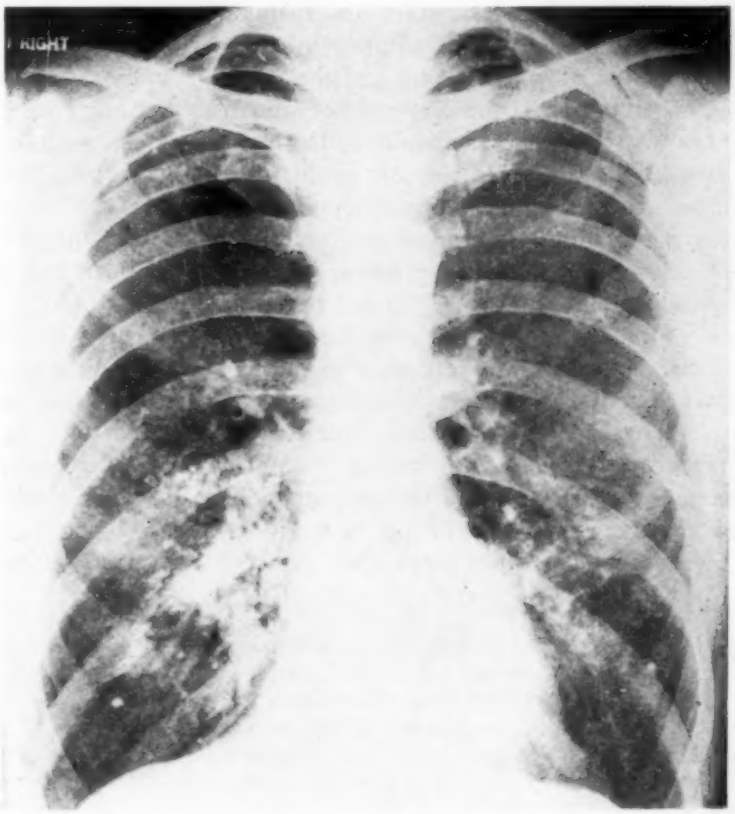


FIG. 2. (Case 1, 12/29/42) Complete reëxpansion of the right lung with cystic areas evident in both upper lobes.

after 15 years of age. The roentgenographic film of the lungs showed evidence of cystic change within both lungs as well as peripheral cysts. This would indicate that the cystic change was not wholly, at least, due to emphysematous bullae. There was no history of asthma as a cause for emphysematous bullae. The lipiodol studies showed no evidence of bronchiectasis. There was no evidence in the history that pneumonitis played any part in the causation of the cysts. The roentgenogram showed a mild degree of silicosis which, however, did not seem to have produced sufficient fibrotic changes in

the lung to cause the cysts. Therefore, it seems most likely that we are dealing with a case of congenital cystic disease of the lung.

The frequent short attacks of dyspnea which the patient experienced were probably due to an increase in air pressure within one or more cysts, so called "tension cysts." The episode of dyspnea and chest pain lasting for three weeks, which occurred at the age of 45, may have been due to a spontaneous pneumothorax which resolved.

Schenck,[2] in his recent review of congenital cystic disease of the lung, states that the occurrence of spontaneous pneumothorax in congenital cystic disease is rare in the adult, more common in children.

The history of exposure to silica and the moderate radiographic changes in the lung fields suggested the diagnosis of silicosis. Spontaneous pneumothorax is known to occur occasionally in this condition, 3.5 per cent in one series.[3] The slight degree of silicosis in this case, however, probably eliminates this as a cause for the spontaneous pneumothorax.

The treatment of this case was similar to the handling of all cases of tension pneumothorax: early aspiration of air because of the patient's severe dyspnea. This, however, did not relieve the patient, and it was assumed, therefore, that the perforation had not had sufficient time to heal. He was placed at rest and watched closely. Two weeks later the removal of 1,000 c.c. of air quickly deflated the pneumothorax and the injection of the patient's blood was done to produce pleural adhesions and prevent, if possible, a recurrence of the pneumothorax. Blood has been successfully used by Watson and Robertson [4] to produce pleural adhesions. Other substances [5] which may be used are 30 to 67 per cent glucose, iodized oil, ½ per cent solution of silver nitrate, oil of turpentine, guaiacol in iodoform, iodized talc, and plain talc.[6]

Case 2. T. A., a 40 year old mechanic, was admitted to Barnes Hospital April 9, 1942. From 1918 to 1924, he had been a coal miner. In 1924 he had had a sudden attack of intense pain in the right side of the chest. The symptoms were severe for several days, then gradually disappeared during the next four months. The patient then remained in good health until June 1941, when he had a sudden attack of severe pain in the anterior part of the left side of his chest, accompanied by a cough and marked dyspnea. He attributed this attack to a severe paroxysm of coughing. The pain gradually disappeared, but the dyspnea persisted up to the time of admission to the hospital.

Physical Examination. Temperature 37.4° C. Pulse 90. Respirations 24. Blood pressure 125 mm. Hg systolic and 80 mm. diastolic. The significant findings were in the chest. There was a marked lag of the left side of the chest, percussion note was hyperresonant throughout the left side, breath sounds and tactile fremitus were absent. The trachea was deviated to the right. The heart was markedly displaced to the right.

Laboratory Findings. Blood count was normal, Kahn reaction negative, and urinalysis negative.

Roentgenographic examination of the chest (figure 3) showed a left-sided pneumothorax with an apparently completely collapsed left upper lobe, and a moderately collapsed left lower lobe which extended to within 3 cm. of the lateral

chest wall. The suspected left upper lobe could be seen as a small dense tumor-like mass in the left hilus region. The heart and mediastinal structures were markedly displaced to the right. Bronchogram of the left chest showed that the left upper lobe bronchus entered the mass noted on the roentgenogram, proving that it was the left upper lobe (figure 4).

Course in Hospital. Because of the dyspnea, 250 c.c. of air were removed from the left side of the chest. Initial pressure was minus 5 centimeters of water, zero; final pressure reading was the same. No expansion of the lung could be demonstrated following the removal of air, nor was there any relief of the patient's dyspnea.

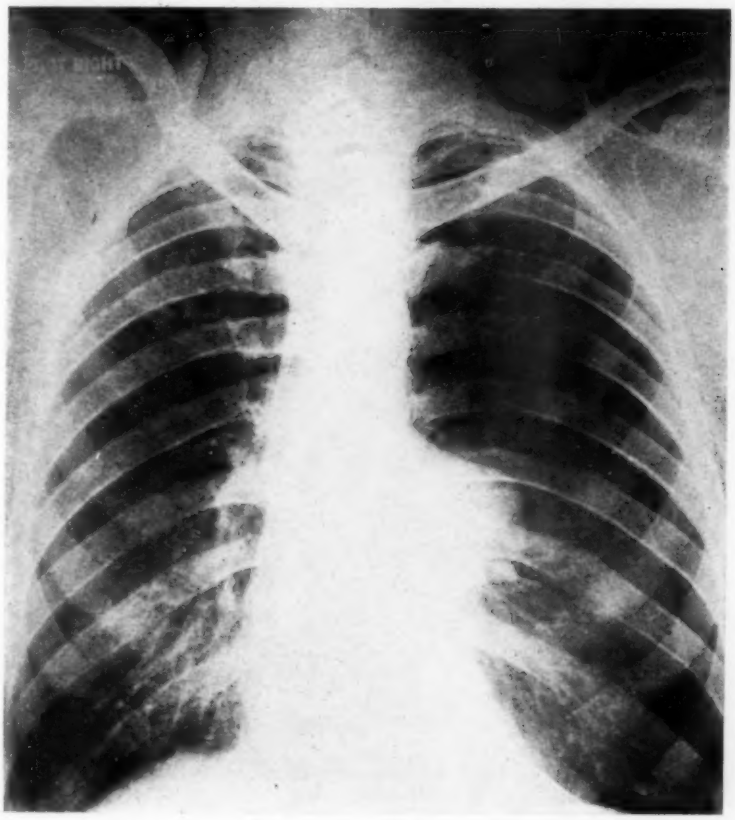


FIG. 3. (Case 2, 4/11/42) Spontaneous pneumothorax with complete collapse of the left upper lobe and partial collapse of the left lower lobe.

Because of the atelectasis, a bronchoscopy was performed on April 20, 1942, at which time the mucosa of the carina was noted to be thickened. A small amount of mucoid secretion was present in the left upper main bronchus. This was aspirated but showed no significant findings. A biopsy of the thickened mucosa showed only small round cell infiltration, no tumor cells.

On April 21, 1942, 400 c.c. of air were removed from the left side of the chest. The initial pressure was plus 2, minus 10 centimeters of water, final pressure, minus 4, minus 7. The patient was discharged on April 22, 1942, without any apparent subjective or objective improvement.

On June 15, 1942, the patient returned to the chest clinic completely relieved of his symptoms. Roentgenographic examination of his chest showed complete expansion of his entire left lung (figure 5). The lung fields were perfectly clear throughout. The patient remained well up to his last observation on January 5, 1943.

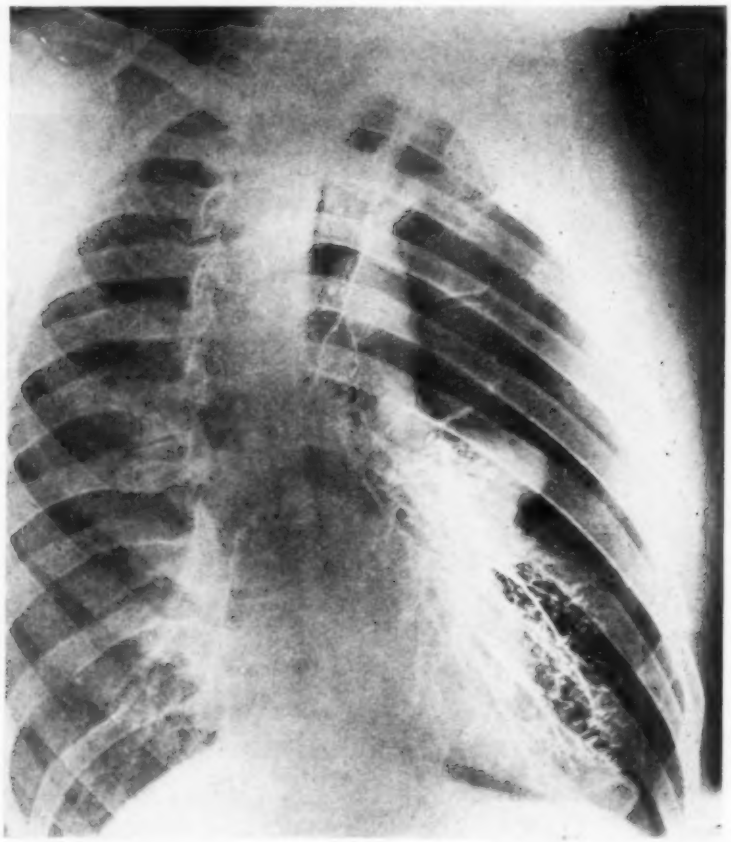


FIG. 4. (Case 2, 4/14/42) Lipiodol bronchogram showing mass to be left upper lobe.

Comment. This is a case of idiopathic spontaneous pneumothorax. The history would indicate that the present attack is of 10 months' duration. Although it is well known that the average case of idiopathic spontaneous pneumothorax clears up within four to eight weeks, a small percentage may remain chronic,[7] even lasting for years, and we feel that this case is of the latter, or chronic type.

The most interesting feature of the case is the complete collapse of the left upper lobe with the relatively mild collapse of the left lower. A similar but less striking picture may be seen in the selective collapse occurring at times during pneumothorax therapy for pulmonary tuberculosis.

J. Palocio and E. S. Mazzei,[8] in 1941, stated that they were the first to report cases of atelectasis occurring during the course of spontaneous pneumothorax. They report four cases. Two of the cases were similar to ours in that one involved only the upper lobe, and the other involved only the lower lobe; the other two were said to show atelectasis of the entire lung. There was a definite difference between these cases and ours in that there was complete recovery in all four cases within 20 days. The author believed that the atelectasis was due to vagal stimulation by the spontaneous pneumothorax.

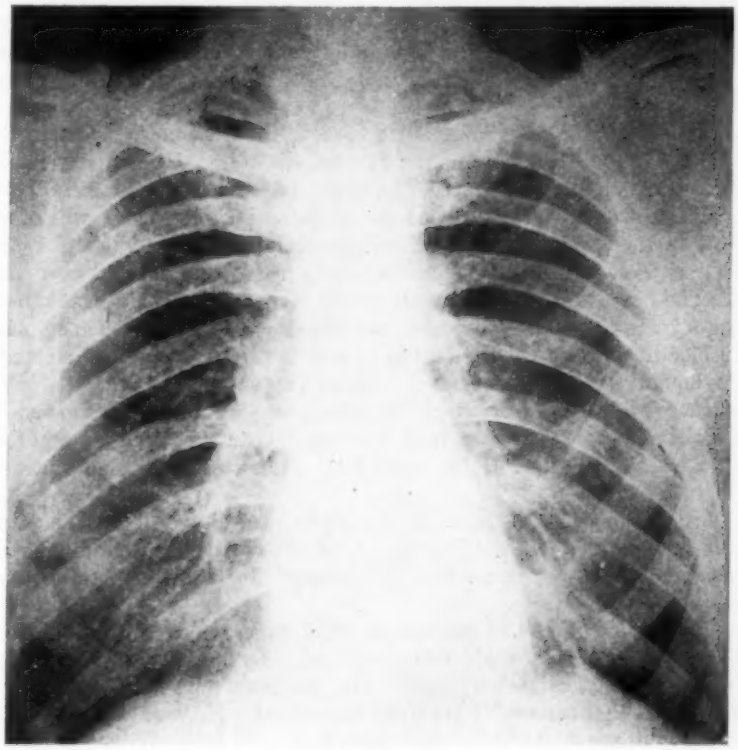


FIG. 5. (Case 2, 6/15/43) Complete reëxpansion of the left lung.

Escudero and Adams[9] have shown that atelectasis produced experimentally in dogs may be followed by spontaneous pneumothorax, probably due to air passing through the anatomically thin mediastinum; but they themselves indicate that this is probably not applicable to human beings.

There are several case reports of postoperative atelectasis, and atelectasis occurring during the course of pneumonia, followed by spontaneous pneumothorax. In all these cases the authors felt that the collapse occurred first and the pneumothorax later. The history in our case would indicate that we are

dealing with a case of primary pneumothorax, as there was no cause for sudden atelectasis.

The complete collapse of the left upper lobe and the subsequent re-expansion following bronchoscopy would suggest that we were dealing with a bronchial obstruction which was relieved by the bronchoscopic procedure. Inasmuch as there was only a moderate amount of mucus removed from the bronchus, we felt that there may have been an additional element in the form of kinking of a bronchus.

Case 3. C. H., a 28 year old engineer, entered Barnes Hospital on May 20, 1942. His past history was noncontributory. On May 19, 1942, while shoveling dirt, he noticed a sudden sharp pain in the upper anterior part of the right side of his chest radiating to his upper abdomen. The pain diminished for a short time but recurred the following day with gradually increasing dyspnea, and he was, therefore, sent to the hospital.

Physical Examination. Temperature 38.2° C. Pulse 95. Respirations 26. Blood pressure 130 mm. Hg systolic and 70 mm. diastolic. The patient appeared ill, was dyspneic and slightly cyanotic. The chief physical findings were confined to the chest. There was a marked lag of the right side of the chest which was tympanitic down to the level of the eighth rib posteriorly, below which the percussion note was flat. The breath sounds and voice sounds were absent over the entire right side. The heart and mediastinal structures were markedly displaced to the left.

Laboratory Findings. Blood count: red blood cells 3,900,000, hemoglobin 78 per cent, white blood cells 12,300; differential count: "stab" forms 18, segmented neutrophiles 56, lymphocytes 23, monocytes 3. Kahn reaction negative.

Roentgenographic examination of the chest on May 21, 1942, showed a hydropneumothorax on the right with a fluid level at the anterior end of the fourth rib. There was a marked collapse of the right lung with a pleural adhesion at the apex (figure 6).

Course in Hospital. On May 20 the right pleural cavity was aspirated and hemorrhagic fluid was obtained. The red blood cell count on the fluid was 5,000,000. The white blood cell count was 8,800. Culture of the fluid was sterile and guinea pig inoculation was negative.

From May 20 to June 1, 1,800 c.c. of fluid were removed from the chest, and at the same time 450 c.c. of air were replaced. By June 6, almost complete re-expansion of the lung had taken place. The patient's temperature was 38° C. for the first five days, then gradually returned to normal. He was discharged from the hospital to the Outpatient Department on June 8.

Fluoroscopic observation on June 13, 1942, showed that the lung had completely expanded, although there was a small amount of fluid at the right base. On July 11, 1942, there was no longer any fluid. On August 8, the patient returned to the clinic when he reported that on July 23, while lifting a studio couch, he suddenly developed a sharp pain in his right chest associated with dyspnea. This lasted 30 minutes. He called his local doctor who took roentgenograms of his chest and found that he had a pneumothorax. Our examination on August 8 showed that he had a right sided pneumothorax with about 50 per cent collapse of the right lung and a small amount of fluid in the right costophrenic angle. He was relatively comfortable at this time. On September 20, 1942, he had a 20 per cent collapse without fluid. On October 17, the lung had completely reëxpanded. Careful study of the lungs following re-expansion showed no clinical or roentgenological evidence of tuberculosis.

Comment. This is a case of spontaneous idiopathic hemopneumothorax, a relatively rare condition. Hartzell [11] states that there were 40 reported undisputed cases of spontaneous hemopneumothorax up to 1942, which with his three cases made 43. There are unquestionably many other unreported cases of which we have seen several. The condition occurs characteristically, as in this case, in the young, healthy adult male.

The accepted opinion of the origin of a spontaneous hemopneumothorax is that it is due to the rupture of a valve vesicle situated near the pleural

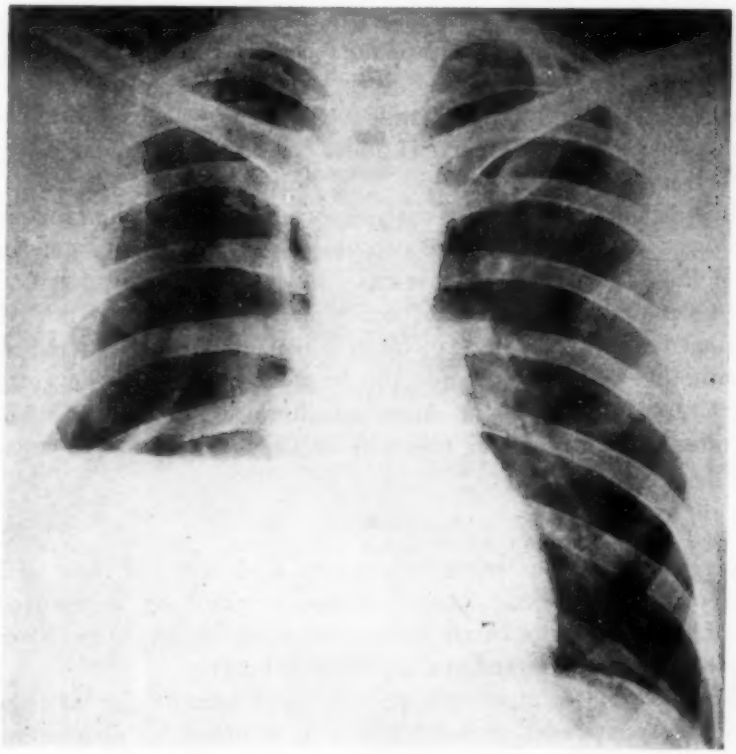


FIG. 6. (Case 3, 5/21/42) Spontaneous hemopneumothorax.

surface, followed by a short period of improvement, then recurrence of pain, dyspnea, and shock-like symptoms, depending, of course, on the amount of blood lost.

The treatment of a case of spontaneous hemopneumothorax must be individualized. When there is a considerable amount of fluid present it is usually wise to remove fluid in order to relieve pressure on the mediastinum. At the same time care must be taken not to reduce the intrapleural pressure too greatly because of the danger of opening up an incompletely healed fistula, and thus causing an increase in the bleeding and of the pneumothorax.

This can be prevented by the introduction of a relatively small amount of air as was done in this case.

The most interesting feature of this case was a recurrence of pneumothorax on the same side approximately six weeks after complete healing of the pneumothorax. Although the second attack of pneumothorax was a moderately severe one, the amount of fluid present was so small that aspiration was not attempted and the fluid quickly disappeared.

Snively et al.[12] state that there are no recorded cases of recurrent spontaneous hemopneumothorax. They state that pleural adhesions following the presence of blood in the pleural cavity make further collapse impossible. Hopkins [13] also states that there are no recorded cases of recurrent hemopneumothorax. He states that the fibrin deposits, or the presence of blood in the pleural cavity, with the resulting sterile pleurisy, lead eventually to the formation of such extensive pleural adhesions that subsequent collapse and bleeding become impossible.

We found that Rist [14] had recently reported a case of spontaneous hemopneumothorax which was followed two years later by a spontaneous pneumothorax on the same side. In this case, however, there was only a small amount of hemorrhagic fluid present originally. Repetti [15] reported a case with a rather large hemorrhagic effusion which showed a recurrent attack of hemopneumothorax 87 days after the first attack. We believe that ours is the first reported case in the American literature of a large spontaneous hemopneumothorax which was followed by a recurrence on the same side.

Summary

A case of spontaneous pneumothorax in a 51 year old male with previously unrecognized congenital cystic disease of the lung is reported. The removal of a large amount of air and the injection of the patient's own blood into the pleural cavity resulted in a rapid clinical cure.

A case of complete atelectasis of the upper lobe of the left lung associated with a spontaneous pneumothorax is recorded. Pneumothorax had been present for 11 months. The collapsed lung rapidly reëxpanded following bronchoscopy, and there was no evidence of disease in the lung following reëxpansion. A careful survey of the literature shows only one previous report of atelectasis following idiopathic spontaneous pneumothorax.

A case of spontaneous hemopneumothorax with recovery followed by a recurrence of the pneumothorax is recorded. This is the third reported case of recurrence of pneumothorax following spontaneous idiopathic hemopneumothorax. It has frequently been stated that adhesions follow hemopneumothorax and prevent recurrence.

BIBLIOGRAPHY

1. SCHENCK, S. G.: Diagnosis of congenital cystic disease of the lung, Arch. Int. Med., 1939, lx, 1–21.
2. SHENK, S. G.: Congenital cystic disease of the lungs, Am. Jr. Roentgenol., 1935, xxxv, 604–629.
3. SOKOLOFF, M. J., and FARRELL, J. T., JR.: Spontaneous pneumothorax in anthrosilicosis, Jr. Am. Med. Assoc., 1939, cxii, 1564–1566.
4. WATSON, E. E., and ROBERTSON, C.: Recurrent spontaneous pneumothorax: report of three cases, Arch. Surg., 1928, xvi, 431.
5. HENNELL, H., and STEINBERG, M. F.: Tense pneumothorax: treatment of chronic and recurrent forms by induction of chemical pleuritis, Arch. Int. Med., 1939, lxiii, 648–663.
6. Unreported Cases.
7. KJAERGAARD, H.: Spontaneous pneumothorax in the apparently healthy, Acta med. Scandinav., supp. 43, 1931, 1–159.
8. PALOCIO, J., and MAZZEI, E. S.: Die Atelektase beim Spontanpneumothorax, Schweiz. med. Wchnschr., 1941, lxxi, 601–602.
9. ESCUDERO, L., and ADAMS, W. E.: Spontaneous pneumothorax associated with massive atelectasis, an experimental and clinical study, Arch. Int. Med., 1939, lxiii, 29–38.
10. SANTE, L. R.: Massive (atelectatic) collapse of the lung with report of a case showing associated spontaneous pneumothorax, Am. Jr. Roentgenol., 1928, xx, 213–217.
11. HARTZELL, H.: Spontaneous hemopneumothorax, report of 3 cases and review of literature, Ann. Int. Med., 1942, xvii, 496.
12. SNIVELY, D., SHAUMAN, H., and SNIVELY, W. D.: Spontaneous hemopneumothorax, report of a case, Ann. Int. Med., 1942, xvi, 349–356.
13. HOPKINS, H. U.: Spontaneous hemopneumothorax: report of 3 cases with a review of the literature, Am. Jr. Med. Sci., 1937, cxciii, 763–772.
14. RIST, E., and WORMS, R.: Sur un cas d'hémopneumothorax spontané, Bull. et. mém. Soc. méd. d. hôp. de Paris, 1940, lvi, 272.
15. REPETTI, L. P.: Secuelas del hemoneumothorax Espontaneo, Semana méd., 1940, ii, 1186–1190.

LUPUS ERYTHEMATOSUS (ERYTHEMATODES) AND OVARIAN FUNCTION: OBSERVATIONS ON A POSSIBLE RELATIONSHIP, WITH REPORT OF SIX CASES *

By EDWARD ROSE, M.D., F.A.C.P., and DONALD M. PILLSBURY, Colonel, M.C., A.U.S., *Philadelphia, Pennsylvania*

THE syndrome which is unfortunately known as lupus erythematosus has been the subject of an enormous literature since Hebra's clinical description, under the name of seborrhea conjestiva, in 1845. The primary etiology and pathogenesis of the disease still remain elusive despite the development of several theories.[1] The use of the term "lupus" was introduced in the latter part of the nineteenth century when the disease was generally considered to be tuberculous. Although opinion is still somewhat divided, a tuberculous etiology has not been established. The term "lupus," therefore, must be regarded as a misnomer, although its use has by this time become so entrenched by custom that abandonment of it may be difficult. Substitution of the term "erythematodes" as suggested by Jadassohn and others [2] would nevertheless appear desirable.

The morbid anatomy, both cutaneous and visceral, as well as the clinical features of the erythematodes syndrome have been thoroughly described.[3] Among the several suggested classifications, that proposed by Urbach and Thomas [4] appears to be simplest and most practical.

Their classification is as follows:

Chronic	discoid
	disseminated
Exacerbated	discoid
	disseminated
Genuine acute (systemic)	acute
	subacute

In the chronic discoid type the cutaneous lesions are usually limited to the cheeks, nose and hands, with occasional involvement of the scalp, forehead, ears and lower anterior neck. The lesions are sharply circumscribed, elevated and reddish in color with frequent silvery scaling beneath which keratotic plugs often extend into hair follicles and the mouths of sebaceous glands. The lesions may remain indolent for many years or they may grow slowly by

* Received for publication July 20, 1944.

From the Endocrine Section of the Medical Clinic and the Department of Cutaneous Medicine, Hospital of the University of Pennsylvania.

Colonel Pillsbury's contribution to this communication preceded his entry into the Army of the United States.

peripheral extension, while central atrophy and scarring develop. Systemic manifestations are uncommon and mild, consisting of occasional slight fever, mild anemia or leukopenia, fatigability and malaise. The chronic disseminated form differs from the discoid chiefly in the widespread distribution of the lesions and in their tendency to increase in size by confluence. The prognosis of these chronic forms is relatively benign and the incidence of improvement or cure has been reported as high as 60 per cent.[5] Females are affected somewhat more often than males (52 to 67 per cent females) and the disease appears most often in young or middle-aged persons. Acute or subacute systemic manifestations occasionally appear.

In the exacerbated forms of discoid or disseminated erythematodes acute inflammatory changes may appear in the erythematous lesions, which may increase rapidly in size and number. In addition, a variety of polymorphic lesions may be seen in the skin and mucous membranes, including bullous, necrotic, ulcerative, crusted, hemorrhagic, papular and pellagroid changes. Such exacerbations may occur without apparent cause or they may follow the removal of focal infection, exposure to cold, ultraviolet or actinic irradiation, burns, trauma, or treatment with gold, bismuth, quinine or carbon dioxide snow. In addition, acute or subacute systemic manifestations may occur. These include fever of irregular type, arthralgia, adenopathy, anemia, leukopenia, thrombocytopenia, splenomegaly, pleurisy, pericarditis and peritonitis with effusion, bronchopneumonia, endocarditis, meningitis, acute ulceration of the gastrointestinal tract and vascular lesions in the retina sometimes accompanied by papilledema. Renal lesions of varying character are likewise common with the urinary excretion of albumin, casts and abnormal numbers of red and white blood cells.[6] The constancy and specificity of the renal lesions, particularly those affecting the glomeruli, are still subject to some differences of opinion [7]; in our experience, however, glomerular damage and terminal renal failure have been strikingly frequent. The endocardial vegetations and myocardial changes have been thoroughly described.[8] Many authorities believe that the atypical verrucous endocarditis described by Libman and Sachs [9] occurs as a variant of, or as a part of the clinical picture in systemic erythematodes. During systemic exacerbations as well as in the chronic phases of the disease pathogenic microörganisms cannot as a rule be recovered from the blood stream. Occasionally, however, one or more of several varieties of pathogens (pneumococci, streptococci, etc.) appear in blood cultures, probably as secondary or terminal invaders.

In the group described by Urbach and Thomas [4] as the genuine acute form, systemic manifestations appear shortly after, or sometimes even before, the onset of the cutaneous lesions. The latter are usually florid, and the systemic manifestations often develop with explosive violence. The entire course of the disease may occupy only a few weeks or months. Occasionally in the so-called subacute variety of this genuine acute form several exacerbations and remissions may be seen. In all types of erythematodes a history

of marked sensitivity to light is common, and violent exacerbations may follow exposure. The prognosis in acute exacerbated, and in the genuine acute forms is very grave, the mortality having been estimated [10] as high as 100 per cent. Occasionally, however, a surprising remission may occur in patients appearing almost moribund. In the subacute systemic types the mortality rate has been estimated at about 50 per cent.[10] The cause of death in systemic erythematodes may be renal failure, bronchopneumonia, meningitis, secondary sepsis, or hyperpyrexia with exhaustion.

The nature of the basic pathological process remains the subject of disagreement. Because of the protean characteristics of the disease and the ubiquitous distribution of its lesions, it has been thought that the fundamental abnormality resides in the vascular system, and the term "visceral angiitis" has been offered as a synonym.[6] As a further refinement the collagen elements of connective tissue have been suggested as the primary locus, and the term "diffuse collagen disease" has been proposed.[11]

The pathogenesis of erythematodes remains obscure. The possible importance of photosensitivity has been mentioned, and in this connection the rôle of porphyrins, particularly those produced in the intestinal tract, has received considerable attention.[12] The importance of infectious-allergic and vasculo-allergic factors has recently been thoroughly considered by Stokes, Beerman and Ingraham.[1] Focal infection, tuberculosis and even lead poisoning have likewise been suggested but without convincing proof. The high mortality in the acute and subacute systemic exacerbations indicates the ineffectiveness of present therapy. A variety of therapeutic agents have been about equally futile; these include sulfonamides, transfusions of whole blood and plasma, vitamins, liver extract, general supportive measures and a number of purportedly specific drugs.

From the foregoing it will be apparent that erythematodes constitutes a syndrome of obscure etiology and pathogenesis in which widespread systemic involvement frequently appears as a grave complication. It is also apparent that no effective therapy has yet been found for the prevention or control of these systemic exacerbations, and that further search for more effective therapeutic measures is necessary. In our experience with the disease *we have been impressed by the striking frequency with which systemic involvement occurs in females during the active sexual phase of life* (i.e., between puberty and the menopause). Systemic exacerbations affect females from three to four times as often as males.[13]

Between January 1930 and May 1944 we have encountered 29 patients presenting evidence of erythematodes with acute or subacute systemic manifestations. Statistical data relating to these patients are shown in tables 1 and 2. From these tables it will be seen that females predominated by more than three to one, and in the genuine acute group by almost six to one. It is also apparent that 21 of the 22 females were in active menstrual life at the time of onset of their disease, and that most of them were below the

TABLE I

Types			Known Dead	Known Living	Fate Uncertain
Acute exacerbated	11	Female	4	3	2
		Male	1	1	0
Genuine acute	13	Female	11	0	0
		Male	2	0	0
Genuine subacute	2	Female	1	0	0
		Male	1	0	0
Uncertain classification	3	Female	0	1	0
		Male	0	1	1
Totals	29	Female (22)	16	4	2
		Male (7)	4	2	1

TABLE II

Age of Onset	Females	Males
10–19	7	0
20–29	12	2
30–39	2	4
40–49	0	1
50–59	0	0
60–69	1	0

age of 30. Our data also emphasize the extremely grave prognosis in the genuine acute type of exacerbation, all of the 13 patients in this group having died. The possible relationship of ovarian function to these types of erythematodes is further suggested by the premenstrual accentuation of chronic discoid and disseminated skin lesions reported by some patients.

Because of the striking sex incidence of the disease and the ineffectiveness of other methods of therapy we were led to employ as early as 1939 large daily intramuscular injections of testosterone propionate (25 mg.) in six acute and subacute cases.* The results were inconclusive. We then conceived the idea of destroying ovarian function, either by irradiation or by oöphorectomy in selected cases of erythematodes. In June 1942 the first of a group of five patients was castrated by oöphorectomy. We later learned that the treatment of erythematodes in the female by castration had previously been reported by others. Contratto and Levene [15] in 1939 reported a case of erythematodes in which irradiation of the ovaries was tried, the patient unfortunately dying of pneumonia before the effects of treatment could be evaluated. Sosman and his associates [16] have employed similar therapy in several other cases but without striking results. Cluxton and Krause [17] have recently mentioned suppression of ovarian function as a possibly useful therapeutic procedure in erythematodes with systemic manifestations. We report below six cases in which the course of the disease was observed following a spontaneous or artificial menopause.

* This therapeutic agent has also been suggested by Baehr.[14]

Case Reports

Case 1. D. G., a white unmarried woman, aged 25, was first admitted to the service of Dr. John H. Stokes at the Hospital of the University of Pennsylvania on September 3, 1938. An eruption had appeared on the cheeks and nose three years previously. This had become steadily worse in the last two years, especially so after a course of irradiation and injections of gold and bismuth four months prior to admission. Afternoon fever and malaise had been noted for several months. In 1936 she had been treated for salpingo-oöphoritis, with surgical drainage of the cul-de-sac. There had been occasional nose bleeds and joint pains since 1934. There was a strong family history of tuberculosis. Examination showed typical erythematous macular lesions of erythematodes on both cheeks, the bridge of the nose and the left ear, with a number of small macular lesions, ascribed to mosquito bites, scattered over the extremities. The tonsils and one molar tooth were infected, and there was evidence of chronic infection in the urethra, cervix and Fallopian tubes. Cervical adenopathy was present. There was a regular, moderate afternoon fever, not exceeding 100° F. There was slight anemia and leukopenia, with a moderate increase in the sedimentation rate of the erythrocytes. Hemolytic *Staphylococcus aureus* was cultured from the urine. An intracutaneous tuberculin test was positive with 0.001 mg. O. T. Roentgenograms of the chest showed a healed primary complex in the right lung. The pelvic infection received local treatment and the infected tooth and tonsils were removed. The patient improved and was discharged on November 6, 1938.

During the following year the facial lesions varied in intensity and several new erythematous plaques appeared on the right cheek. Her treatment included several series of injections of bismuth and gold salts and sulfonamides. In November 1939 weakness and malaise increased and low grade fever with occasional chills was noted. The patient was readmitted to the hospital November 29, 1939. At this time the skin lesions had extended to both ears and the right supraorbital region. There was widespread adenopathy, and prominence of the superficial veins was noted over the neck and thighs. Evidence of pelvic infection was still present in addition to cystitis and left-sided pyelitis. Moderate anemia, leukopenia and increased sedimentation rate of the erythrocytes were still present. The patient remained in the hospital until July 4, 1940. During this time there were repeated exacerbations and remissions affecting both the cutaneous lesions and her general condition with irregular fever most of the time. Treatment included sulfanilamide, the injection of autogenous vaccines and estrogens, urinary antiseptics, dilatation of the left ureter by catheter and finally testosterone propionate. Estrogen therapy seemed to make the erythematodes worse, and severe general reactions followed each ureteral dilatation, so that these measures were soon abandoned. Within two weeks after institution of testosterone therapy, marked general improvement occurred and the patient was in complete remission when discharged July 4, 1940.

In August 1940 and again in January 1941 she suffered attacks of otitis media, the last one associated with "grippe." In September 1940, tender erythematous areas appeared on the forearms. In March 1942, there was lumbar backache and urinary frequency. The facial lesions remained quiescent until March 1942 when there was a marked increase in redness and swelling. She was readmitted to the hospital April 14, 1942, for consideration of castration. At this time the cutaneous lesions on the face and ears were florid and lesions were present on the arms which closely resembled tuberculids. There was slight enlargement of the spleen and liver, cervical adenopathy, anemia, leukopenia, and increased sedimentation rate of the erythrocytes. Infection of the left kidney and bladder was still present. Roentgenograms of the chest now showed bilateral apical lesions presumably tuberculous. No tubercle bacilli, however, could ever be found in the sputum. A tender mass was palpable in the left adnexa. On June 1, 1942, under spinal anesthesia, the uterus, both ovaries and tubes

were removed. The specimens showed chronic oöphoritis and salpingitis but no histological evidence of tuberculosis. Her postoperative convalescence was uneventful except for an acute exacerbation of pyelocystitis which soon responded to urinary antiseptics. The cutaneous lesions began to improve within two weeks after the operation and by August 1942 all evidence of activity had disappeared leaving only scarring.

The patient has been seen regularly at intervals of three months since operation. Except for occasional migrainous headaches, hot flashes, and one or two acute episodes of lumbar backache she has remained entirely well. She has gained 25 pounds and has been regularly employed in a shell loading plant. In November 1942 she was briefly exposed to intense light from a burning signal flare and for a few weeks thereafter there was a slight recurrence of erythema on the left cheek. With this exception the cutaneous lesions have remained entirely in abeyance. Repeated roentgenograms of the lungs have shown no significant change in the apical lesions. Moderate left cervical adenopathy is still present with calcification in some of the nodes. At the time of her last examination (April 25, 1944) there was moderate anemia and a slight increase in the sedimentation rate of the erythrocytes. Her temperature has not exceeded 99° F. at any examination since her last discharge from the hospital.

Comment. This 25 year old white woman presented the picture of recurrent acute and subacute exacerbations of chronic discoid (disseminated?) erythematodes with moderate evidence of systemic involvement. Her disease was complicated by infection in the urinary tract, pelvic organs, teeth and tonsils and by probable pulmonary tuberculosis. Some of the cutaneous lesions on the extremities may have been tuberculids. After an irregular course, without substantial improvement, extending over almost six years she has shown very striking improvement with practically complete disappearance of cutaneous lesions as well as a marked gain in general health following the removal of her uterus, tubes and ovaries. So far as we are aware this is the first reported instance in which surgical castration has been performed as part of the treatment of erythematodes. The possible importance of the salpingitis, as well as of the urinary tract infection, in maintaining the activity of the erythematodes cannot be overlooked. We must admit the possibility that the removal of the Fallopian tubes, and the subsidence of the urinary tract infection, may have been important factors in this patient's improvement. It is interesting to note that her improvement has been maintained despite the absence of significant change in the roentgenographic appearance of the pulmonary lesions.

Case 2. In 1934, V. A., an unmarried colored woman, at the age of 35 began to notice intermittent pallor and blueness of the right third and fourth toes associated with spasmodic pain on walking; several small hemorrhagic areas were noted soon afterward on the affected toes. She remained well after the subsidence of these symptoms until the winter of 1935–1936, when cramp-like pains were noted during sleep in the calves of both legs. Shortly afterward intermittent pain, pallor, mottling, redness and cyanosis of the fingers appeared. These symptoms were more marked in moderate than in cold temperatures, and were alleviated during menses. In March 1937 there was abrupt onset of diarrhea, anorexia, fatigue and pain in the left shoulder followed by cramp-like epigastric pain. She was admitted to the New Haven Hospital where examination showed fever, abdominal distention, and essentially normal blood count, and roentgenographic evidence of left ventricular enlargement and infiltration in the left lower lung. The signs and symptoms subsided promptly and she was discharged after three days. One month later numbness and pain appeared in the fingers with redness and ecchymotic spots over the distal phalanges. On July 6, 1937, she was first admitted to the Hospital of the University of Pennsylvania under the care of Dr. E. M. Landis. The principal findings included moderate irregular fever, abdominal distention with epigastric pain and

tenderness, and slight enlargement of liver and spleen; the heart was overactive and slightly enlarged to percussion, with a loud blowing systolic murmur audible over the entire precordium and transmitted into the left axilla. Movement of the right diaphragm was limited. The right dorsalis pedis pulse could not be felt. Several reddish nodules were scattered over the anterior surface of both lower legs and there were a few splinter hemorrhages under the fingernails. Several elevated erythematous plaques were scattered over the cheeks and lower thighs. The sedimentation rate of the erythrocytes was increased to 35 mm. per hour. There was moderate anemia (hemoglobin 49–78 per cent) and leukopenia (leukocytes 5700 to 9000 per cu. mm.). Platelet counts were normal. Blood cultures remained sterile, but *Streptococcus mitis* was recovered from the urine. No foci of infection could be found in the upper respiratory tract, teeth, pelvis or gastrointestinal tract. Signs and symptoms gradually subsided and the patient was discharged still showing quiescent erythematous facial lesions, with a tentative diagnosis of lupus erythematosus with acute systemic manifestations.

During the winter of 1937–1938 the facial lesions fluctuated in intensity and several new erythematous lesions appeared on the hands and legs. Showers of petechiae appeared occasionally on the extremities and abdomen and on at least one occasion these were associated with symptoms suggesting hemorrhage or infarction in the spleen and left lung. The patient was easily tired, slightly anemic and often mildly febrile. Her menses became increasingly profuse. On August 11, 1938, a supravaginal hysterectomy was performed by the late Dr. P. B. Bland at the Jefferson Hospital because of a fibroid tumor of the uterus. The ovaries were not removed. A postoperative pulmonary complication was reported as the result of embolism.

During the following winter the patient remained in fair health although continuing somewhat anemic and with intermittent painful dusky lesions on the fingers. No fresh skin lesions were noted until January 1942 when some scaling and extension of the facial lesions were observed. In March 1942 the patient was readmitted to the Hospital of the University of Pennsylvania with streptococcal bronchopneumonia and hemolytic streptococcic bacteremia. At this time there was some anemia, leukopenia and thrombocytopenia (platelets 80,000 per cu. mm.). Fresh disseminated erythematous and bullous lesions appeared on the face, lips, ears, scalp and extremities. The patient was desperately ill for several days but improved gradually following the use of sulfadiazine, testosterone and blood transfusions.

Irregular menstrual bleeding had continued after the hysterectomy. In the summer of 1942 hot flashes and sweats appeared and the menstrual bleeding became scantier and less frequent. Coincidentally with these menopausal manifestations there was marked improvement both in the appearance of the cutaneous lesions and in the patient's general health. Since that time she has been able to continue her work as a physician with few interruptions, and no severe exacerbations have appeared. She has remained mildly anemic with occasional febrile episodes and from time to time there have been scattered, painful petechiae and tender erythematous nodules over the lower anterior legs. The facial lesions, however, have remained quiescent. Because occasional slight vaginal bleeding still recurred at irregular intervals irradiation of the ovaries was advised in October 1943 for the purpose of suppressing menstruation permanently. Because of the demands of her professional work the patient was unable to follow this suggestion. Her last menstrual bleeding occurred January 1944.

Comment. This negro woman, now 45 years old, has survived seven years of repeated acute and subacute systemic exacerbations of disseminated erythematodes. The onset of recognizable cutaneous lesions was preceded by three years of vague ill

health associated with peripheral vasomotor signs and symptoms, somewhat simulating Raynaud's disease. Petechial and nodose erythematous lesions have been prominent. General improvement appeared coincidentally with the manifestations of a natural menopause.

Case 3. M. V., a 26 year old white married woman, had received treatment intermittently since 1936 for discoid erythematodes involving the cheeks, nose and ears. She frequently noted a premenstrual intensification of the erythematous lesions. In 1941 she was treated for an acute illness which was diagnosed as rheumatic fever; a younger brother had had an attack of rheumatic fever also. In the summer of 1942 she began to lose weight and during the following year her weight fell from 125 to 86 pounds. In May 1943 she noted pain and swelling in the left ankle. This was followed by fugaceous pain in various other joints, "pleuritic" pains in the chest, epigastric distress, palpitation, anorexia, malaise and fever. There was, however, no increase in the severity of the cutaneous lesions during this time. On August 14, 1943, she was admitted to the Delaware Hospital in Wilmington, Delaware, under the care of Dr. Edgar Miller, where she remained until October 16, 1943. During this time the cutaneous lesions remained quiescent but there was irregular fever up to 102° F. until September 19, after which time her temperature remained virtually normal. The patient was cachectic and weak with typical lesions of discoid erythematodes involving the cheeks, nose and ears. There was bilateral cervical adenopathy. The heart was markedly enlarged with a moderately loud apical systolic murmur and an occasional presystolic gallop. The rate was rapid much of the time. A transitory pericardial friction rub persisted for about five days. A moderate left pleural effusion appeared, but did not recur after the second aspiration. The liver was slightly enlarged but the spleen could not be palpated. Both eyes showed marked chorio-retinal vascular degeneration and optic neuritis with papilledema; these lesions progressed steadily and vision was eventually lost. Moderate hypertension was present most of the time, the systolic pressure varying from 125 to 180 mm. Hg and the diastolic from 80 to 120 mm.

The principal laboratory findings included a moderate fixed reduction in the specific gravity of the urine, with the excretion of varying amounts of albumin, hyaline and granular casts, and the occasional presence of erythrocytes. The sedimentation rate of the erythrocytes was increased to 30 mm. per hour. There was moderate anemia, the hemoglobin varying from 60 to 80 per cent, and the red cells from 3.1 to 4 million; the leukocyte counts varied from 6,100 to 14,200. The blood urea nitrogen ranged from 9 to 22 mg. per 100 c.c. The total serum protein varied from 5.0 to 7.9 gm. per cent. Blood Wassermann and Kahn reactions were negative. Three blood cultures remained sterile.

Except for a reaction following a blood transfusion on August 23 the patient's condition remained essentially unchanged until her temperature returned to normal on September 19. From this time until her discharge October 16, she remained afebrile, and her strength and appetite gradually improved. Her hypertension persisted, however, and her vision deteriorated. She was seen in consultation by one of us (E. R.) on September 12, at which time therapeutic castration was suggested, despite the fact that she had not menstruated since June 1943. Oöphorectomy was not considered justifiable because of her poor general condition. Therefore, irradiation of the ovaries was employed, and a menopausal dose was given in five installments between September 18 and 27. Following her discharge from the hospital, evidence of progressive renal failure soon appeared and death occurred as a result of uremia two months later.

Comment. This 26 year old woman gave a history of premenstrual local exacerbations of discoid erythematodes for several years, followed by a subacute systemic exacerbation without corresponding intensification of the cutaneous lesions.

Pericardial, pleural and renal involvement dominated the systemic syndrome. The renal damage which caused her death was probably well advanced by the time irradiation of the ovaries was begun.

Case 4. J. F., a white unmarried woman, aged 24, was admitted to the Hospital of the University of Pennsylvania under the care of Dr. B. I. Comroe on January 11, 1943, and remained until January 20, 1943. Since 1940 she had complained intermittently of malaise, fatigue, occasional slight fever and migratory arthralgia. In June 1942 an erythematous facial eruption had appeared following prolonged exposure to the sun. This had persisted with varying intensity, and a diagnosis of lupus erythematosus had been made. Acute painful swelling of the right upper eyelid with conjunctival injection occurred on two occasions. In December 1942 she suffered an acute attack of left-sided pleurisy, following which low grade fever had persisted and arthralgia had recurred. On admission she complained of pain and stiffness involving the ankles, knees, elbows, toes and fingers. Examination showed typical lesions of erythematodes involving the cheeks and nose. There was slight fever, evidence of moderate weight loss, cervical and axillary adenopathy, a left-sided pleural effusion and a systolic murmur over the base of the heart. The blood pressure varied from 120 mm. Hg systolic and 80 mm. diastolic to 140 mm. systolic and 90 mm. diastolic. The urine contained varying amounts of albumin and moderate numbers of leukocytes; culture of the urine yielded hemolytic *Staphylococcus albus*. The hemoglobin varied from 73 to 80 per cent, the leukocyte count from 5,500 to 7,800 per cu. mm. The blood uric acid was slightly increased (4.9 mg. per 100 c.c.) The blood urea nitrogen was 9 mg. per 100 c.c. The urea clearance was normal (90 per cent of average normal function), but the phenolsulphonephthalein excretion was reduced to 34 per cent in two hours. Intravenous urography with Diodrast showed evidence of impaired tubular function. The pleural effusion on aspiration was found to be bacteriologically negative.

The diagnosis of erythematodes with systemic involvement was confirmed by Dr. John H. Stokes. Surgical castration was advised but was declined by the patient's father, who was a physician. Ovarian irradiation was accepted, and this therapy was carried out between February 24 and March 11, 1,000 r units being delivered to each ovary. The patient's menses, previously normal, recurred only once after irradiation.

She was readmitted to the hospital June 13, 1943. During the interval there had been definite recession of the facial lesions, but her general condition had not improved. There were intermittent fever, fluctuating hepatomegaly, recurrence of the pleural effusion, and progressive anemia. Marked albuminuria was almost constant and large numbers of casts, leukocytes and erythrocytes continued to appear in the urine. On readmission there was generalized edema, with bilateral pleural effusion, severe anemia without leukocytosis (hemoglobin 59 per cent, leukocytes 5,900 per cu. mm.), and a temperature of 103° F. The blood urea nitrogen had risen to 70 mg. per 100 c.c., and the serum protein was 5 gm. per cent. Several blood transfusions and general supportive treatment proved unavailing and she was discharged June 19 unimproved. She died at home of renal failure on July 6, 1943.

Comment. This 24 year old patient first developed the cutaneous lesions of erythematodes after two years of vague ill health and intermittent fever with migratory arthralgia. Systemic involvement became manifest six months later, and her clinical course was marked by progressive renal damage which was the principal cause of her death. As in case 3, it seems probable that renal damage was well advanced by the time ovarian irradiation was begun.

Case 5. V. H., a white married woman, aged 37, was first seen April 6, 1943. She had received treatment intermittently by local irradiation and various other means during the preceding five years for discoid erythematodes limited to the face and forehead. There had never been any evidence of systemic involvement. Her

menses had always been normal, and there had been no premenstrual aggravation of the cutaneous lesions. Except for the erythematodes and bilateral cervical adenopathy, physical examination was negative. There was slight leukopenia (leukocytes 5,500 per cu. mm.), but no anemia or thrombocytopenia. The sedimentation rate of the erythrocytes was slightly increased. A menopausal dose of irradiation was delivered to the ovaries in April, after which she menstruated only once. Menopausal symptoms of moderate severity followed. The last report from the patient was received November 3, 1943, at which time she stated that there had been no change in the appearance of the cutaneous lesions.

Case 6. M. F., a white married woman, aged 40, had suffered her first outbreak of erythematodes on the face and neck soon after the birth of her first child at the age of 26. The lesions subsided after two years of local treatment but recurred after the birth of her second child at the age of 32. Since that time the erythematous lesions had remained intermittently active with regular premenstrual exacerbations. There had never been any evidence of systemic involvement. Her menstrual periods had always been regular, but became increasingly profuse and at the age of 35 the right ovary and tube were removed. Following this operation the menses became less profuse but continued regular, and the premenstrual cutaneous exacerbations persisted. Various local methods of treatment had been of no avail. Physical examination showed characteristic erythematodes involving the face and neck with bilateral posterior cervical adenopathy. The blood count was not remarkable. Roentgenograms of the lungs showed a calcified lesion in the right upper lobe. There was no evidence of systemic involvement. A menopausal dose of irradiation was delivered to the left ovary in February 1943 after which menstruation ceased. The cutaneous lesions improved markedly until September 1943. At this time a moderate exacerbation accompanied by slight fever followed an acute pharyngitis. The exhibition of small doses of sulfadiazine was followed by a remission. The erythematodes remained quiescent until January 1944 when another flare-up followed the appearance of two dental abscesses. Since that time the cutaneous lesions have shown recurrent activity but no systemic manifestations have appeared.

Discussion

It is obvious that the cases described above present neither proof of a relationship between ovarian function and erythematodes, nor clear-cut evidence of the efficacy of castration in controlling the disease. The most striking results were observed in case 1, but in this patient the coincidental removal of pelvic infection may well have been an important factor. In case 2, definite improvement, but not complete remission, followed a natural menopause. In cases 3 and 4, the renal lesion which ultimately caused death was probably well initiated before castration was undertaken, and in that respect may not have presented a fair trial for the procedure. Even though definite proof of a relationship between ovarian function and erythematodes could be established, it would not necessarily follow that the ovarian hormones constituted the only, or even a major, etiologic factor. Stokes, Beerman and Ingraham [1] have emphasized the importance of infectious-allergic and vasculo-allergic factors in the pathogenesis of erythematodes. They mention the possible importance of gonadal hormones and "menotoxins" in contributing to cutaneous vasodilatation and thus perhaps increasing cutaneous sensitivity to actinic irradiation as well as infectious and other

allergens. It is conceivable that ovarian hormones might act as sensitizing agents, that they might produce cutaneous vasodilatation, or that they might play an intermediate part in the production of a toxic agent.

Since the lesions of erythematodes have so far not been reproducible in lower animals, the experimental approach to an understanding of its etiology and pathogenesis has not been possible. Further evidence relating to a possible rôle of gonadal function might be obtained by the following methods: (*a*) determination of the androgen-estrogen ratio, the urinary excretion of 17-ketosteroids, and the urinary excretion of pituitary gonadotropic hormones in patients of both sexes during exacerbations and remissions; (*b*) a statistical study, in a numerically significant group of cases, of the effect of castration in preventing systemic exacerbations, compared with a control group; (*c*) histologic study and correlation of changes found in the gonads and other endocrine organs of patients with erythematodes coming to necropsy; (*d*) production or reproduction of systemic exacerbations by the administration of gonadal steroid hormones. Some of these procedures would appear to be ethically unjustifiable at present. At best, the collection of significant data by any of these methods would be handicapped by the relative infrequency with which systemic manifestations of the disease are encountered.

The demonstration of a decreased androgen-estrogen ratio, or an increase in pituitary gonadotropin production in males with systemic involvement might be considered as evidence supporting the rôle of estrogens in the pathogenesis of erythematodes. We have had an opportunity to measure the urinary 17-ketosteroids, gonadotropic and estrogenic substances in a 26 year old male, during an acute systemic exacerbation of the disease. There was no clinical evidence of gonadal or other endocrine dysfunction. The urine contained 7.52 mg. of true 17-ketosteroids per 24 hours (normal 10 to 19 mg. per 24 hours), 100 to 150 mouse units of estrogen, and 50 mouse units of gonadotropin in 24 hours by uterine weight assay (50 to 75 m.u. by vaginal smear, and less than 10 m.u. by ovarian weight). These estrogen levels are well within the normal range for adult males and the gonadotropin as measured by uterine weight responds to somewhat above the usual normal for males. These findings indicate a probable reduction in androgen-estrogen ratio with an increase in gonadotropic pituitary activity. The observations of Selye and others [18] upon the experimental production of renal lesions, followed by hypertension, after the administration of adreno-cortical steroids are of interest in view of the frequency of glomerular lesions and hypertension in erythematodes. In this connection physiologic resemblances of progesterone to the adrenocortical steroids come to mind.

If it be granted that a reasonable argument exists for a further trial of so radical a procedure as castration of the female in an effort to prevent or control systemic exacerbations in erythematodes, the technic and timing of

the procedure require consideration. Oöphorectomy would appear the surest method of eliminating permanently all ovarian hormones, provided the surgical risk appears justifiable in a given case. Menopausal doses of irradiation probably do not suppress ovarian function immediately, and most patients menstruate at least once after the completion of such therapy. The danger of provoking or aggravating systemic involvement by irradiation of the pelvic area would not appear to be great enough to contraindicate the procedure. In genuine acute or subacute exacerbations, in which the systemic phenomena appear coincidentally with, or soon after, the cutaneous lesions, the patient is usually so sick that laparotomy presents too grave a hazard to be justifiable. The optimal indications for castration would appear to be (*a*) in women with a history of premenstrual aggravation of the cutaneous lesions, and with mild systemic phenomena (slight fever, anemia, leukopenia, adenopathy, arthralgia, malaise, etc.) and (*b*) in women in active menstrual life who have shown one or more systemic exacerbations with intervening remissions. A period of remission would obviously appear to be the optimal time for castration.

In conclusion, it should be emphasized that the evidence which we have cited, although perhaps suggestive, is still far from proving that ovarian hormones play a part in the pathogenesis of erythematodes. Elective castration in a woman of child-bearing age or potentiality is a serious procedure, to be justified only if it offers some reasonable hope of improving an otherwise grave prognosis and then only with the full understanding of the patient. Nevertheless, it would appear from the evidence which we have discussed that further investigation of the possible relationship between the gonadal hormones and the pathogenesis of erythematodes is desirable. Our observations have been presented with the hope that they may stimulate such investigation.

Summary

The clinical and pathological features of erythematodes (lupus erythematosus), and various theories relating to its pathogenesis have been briefly reviewed. Statistical data, collected from the literature and from 29 cases of our own, have been cited to illustrate (*a*) the striking frequency with which the systemic manifestations of erythematodes affect females within the active sexual phase of life; and (*b*) the failure of previous therapeutic measures.

The effects of castration or natural menopause upon the course of the disease have been described in six cases. Among these is the first patient known to us in whom oöphorectomy has been employed in the treatment of erythematodes. Measurements of urinary 17-ketosteroids, estrogens and gonadotropins in a male with erythematodes have been reported, which suggest a decreased 17-ketosteroid: estrogen ratio, and increased pituitary gonadotropic activity. The desirability of further investigation of gonadal function in the syndrome of erythematodes has been emphasized.

We are indebted to Drs. E. M. Landis, Edgar Miller, B. I. Comroe, E. P. Pendergrass, and Erich Urbach for permission to report Cases 2, 3, 4, 5 and 6, and to Dr. Olive Hoffman for performing the determinations of urinary 17-ketosteroids, estrogens and gonadotropins.

BIBLIOGRAPHY

1. Stokes, J. H., Beerman, H., and Ingraham, N. R., Jr.: The "lupus erythematosus" concept: an attempt at integration, Am. Jr. Med. Sci., 1944, ccvii, 540.
2. Jadassohn, J.: Mracek's Handbuch der Hautkrankheiten, 1904, iii, 319 (Quoted by Urbach and Thomas [4]).
3. (*a*) Rose, E., and Pillsbury, D. M.: Acute disseminated lupus erythematosus—a systemic disease, Ann. Int. Med., 1939, xii, 951.
   (*b*) Reifenstein, E. C., Reifenstein, E. C., Jr., and Reifenstein, G. H.: A variable symptom complex of undetermined etiology with fatal termination, including conditions described as visceral erythema group (Osler), disseminated lupus erythematosus, atypical verrucous endocarditis (Libman-Sachs), fever of unknown origin (Christian), and diffuse peripheral vascular disease (Baehr and others), Arch. Int. Med., 1939, lxiii, 553.
   (*c*) Banks, B. M.: Is there a common denominator in scleroderma, dermatomyositis, disseminated lupus erythematosus, Libman-Sachs syndrome and polyarteritis nodosa? New England Jr. Med., 1941, ccxxv, 433.
4. Urbach, E., and Thomas, C. C.: Classification and definition of the clinical varieties of erythematodes (lupus erythematosus) with particular reference to its acute and subacute course, Brit. Jr. Dermat., 1939, li, 343.
5. O'Leary, P. A.: Symposium on lupus erythematosus, Proc. Staff Meet. Mayo Clin., 1940, xv, 686.
6. Krupp, M. A.: Urinary sediment in visceral angiitis (periarteritis nodosa, lupus erythematosus, Libman-Sachs "disease"); quantitative studies, Arch. Int. Med., 1943, lxxi, 54.
7. Keith, N. M.: Symposium on lupus erythematosus, Proc. Staff Meet. Mayo Clin., 1940, xv, 682.
8. Gross, L., and Friedberg, C. K.: Nonbacterial thrombotic endocarditis, classification and general description, Arch. Int. Med., 1936, lviii, 620.
9. Libman, E., and Sachs, B.: A hitherto undescribed form of valvular and mural endocarditis, Trans. Assoc. Am. Phys., 1923, xxxviii, 46.
10. Montgomery, H.: Symposium on lupus erythematosus, Proc. Staff Meet. Mayo Clin., 1940, xv, 678.
11. Klemperer, P., Pollack, A. D., and Baehr, G.: Diffuse collagen disease; acute disseminated lupus erythematosus and diffuse scleroderma, Jr. Am. Med Assoc., 1942, cxix, 331.
12. Urbach, E.: Schwerste Lichtdermatosen auf Grundlage von isolierter pathologischer Porphyrinbildung im Darme infolge Dysbakterie und Hepatopathie, Klin. Wchnschr., 1938, xvii, 304–310.
13. Mattras, A.: Zur Symtomatologie und Klinik tödlich verlaufender Fälle von Lupus erythematosus, Arch. f. Dermat. u. Syph., 1938, clxxvii, 223.
14. Baehr, G.: In Text Book of Medicine by R. S. Cecil, 1943, W. L. Saunders, Philadelphia and London, p. 461.
15. Contratto, A. W., and Levene, S. A.: Acute lupus erythematosus disseminatus; report of case, New England Jr.. Med., 1939, ccxxi, 602.
16. Sosman, M.: Personal Communication.
17. Cluxton, H. E., Jr., and Krause, L. A. M.: Acute lupus erythematosus disseminatus; Ann. Int. Med., 1943, xix, 843.
18. Selye, H.: Production of nephrosclerosis by overdosage with desoxycorticosterone acetate, Canad. Med. Assoc. Jr., 1942, xlvii, 515.

CASE REPORTS

LIGATION OF PATENT DUCTUS ARTERIOSUS IN THE PRESENCE OF AN APPARENT BACTERIAL ENDOCARDITIS; REPORT OF CASE APPARENTLY CURED *

By Ralph B. Bettman, M.D., and William Tannenbaum, M.D.,
Chicago, Illinois

The feasibility of ligation of a patent ductus arteriosus was first demonstrated by Gross.[1] The fact that ligation of a patent ductus arteriosus in the presence of what appears to be a bacterial endocarditis may result in the cure of the disease was definitely established by Touroff [2] and confirmed by several other reports.

However, inasmuch as medicine operates very much as law, on the basis of precedent, it will take an accumulation of statistics from many cases before the medical profession in general will become cognizant of this new therapeutic procedure. We, therefore, think it wise that for the next year or two we publish our results of ligation of patent ductus in the presence of bacterial endocarditis as these cases pass through our hands.

Case Report

F. Z., age 18, entered the hospital August 1942, with the history of chills, fever, and extreme malaise. Since early childhood she had had difficulty in breathing on exertion, and had been under observation in one of our Chicago clinics with the diagnosis of a congenital heart malformation, probably a patent ductus arteriosus. From the age of 10 she had attended the Spaulding school for invalid children where she got along well except for the dyspnea on exertion. As a baby she had "rheumatic fever," and in January 1942 had a "streptococcus infection of the lower lip." Except for the above mentioned conditions she had been in fairly good health until July 1942, when she suddenly became sick with a chill followed by high fever. Chills and fever had persisted a month, in spite of sulfathiazole treatment, before she was brought to Michael Reese Hospital. Here the diagnosis of bacterial endocarditis and a patent ductus arteriosus was confirmed and a ligation of the ductus advised. It was not until October, however, that the consent of her legal guardians could be obtained. During this stay in the hospital she ran irregular fever, at times as high as 105° F., with short intermissions of a day or two of nearly normal temperature.

Physical examination on admission to the hospital showed the following relevant findings. The patient was a sickly looking, pale-faced young girl lying listlessly in bed. She was despondent and remained so throughout her preoperative period. She was not cyanotic. When quiet in bed her respirations were normal and easy. She was dyspneic on exertion. There was a slight asymmetry of her chest, the left side

* Received for publication January 28, 1943.
From the Surgical and Medical Services of Michael Reese Hospital.

being more prominent than the right. The heart was enlarged to the left on palpation and percussion. There was a loud systolic murmur, most pronounced over the pulmonic area, followed by a loud diastolic murmur transmitted down the left sternal border to the apex. There was a marked palpable thrill over the entire left chest. Capillary pulsation of lips and fingernails was observed. The spleen was palpable but not tender.

The blood pressure was the same in both arms, 120 mm. Hg systolic and 60 mm. diastolic. The first blood count showed 3,620,000 red blood cells, 10,550 white blood cells, 82 per cent polymorphonuclears, 11 per cent lymphocytes, 7 per cent monocytes, slight hypochromia, moderate anisocytosis, hemoglobin 72 per cent. Subsequent blood counts were surprisingly similar. Urinalysis and blood chemistry were approximately normal. Circulation time was not abnormal. Blood culture was positive for *Streptococcus viridans*. Roentgenographic examination of the chest showed an enlarged heart, a cardiothoracic ratio of 11.7/22.5, and increased convexity of the left heart border.

The electrocardiogram was inconclusive. Cardiac sound tracings confirmed the machinery murmur heard on auscultation.

On October 19, operation to ligate the ductus was undertaken. We followed the usual technic of an anterior incision into the left thoracic cavity, incising the mediastinal pleura over the aorta and demonstrating the arch of the aorta, the left pulmonary artery and the vagus nerve. The site at which the recurrent laryngeal nerve dips under the arch of the aorta marks the lateral border of the ductus arteriosus. The left pulmonary artery was greatly enlarged. The ductus arteriosus measured about 0.5 cm. from the pulmonary artery to the aorta and about 1.5 cm. in diameter. It is of interest to note that the palpable thrill accompanying each heart beat stopped the moment the ductus was compressed. In fact, had there been any doubt of the diagnosis of a patent ductus, it would have been immediately dispelled by this dramatic disappearance of the thrill. For anyone not familiar with the anatomy of this portion of the chest, the site at which the digital pressure can interrupt the thrill will be an excellent guide to the position of the ductus. Although there was a good deal of inflammatory reaction in the region of the root of the lung, we had very little difficulty in isolating the ductus and passing two ligatures of heavy braided silk around it. Before tying the ligatures they were pulled taut and the patient carefully observed lest because of some other unsuspected abnormality ligation of the ductus might not be tolerated. As soon as the ductus was shut off the thrill stopped, but otherwise there seemed to be no change in the patient's condition, and the blood pressure was essentially unchanged. The ligatures were now tied, one as close to the pulmonary artery, the other as close to the aorta as possible. The chest was closed without drainage. The procedure was much simpler than it would appear to have been from the above description; the entire procedure took less than an hour from the beginning of the anesthesia to the time the patient left the table.

The patient was placed in an oxygen tent after operation and kept there for four days. The convalescence was uneventful except for a period of 24 hours starting the day after operation. During this period the patient had a severe chill, a fever of 103.8° F. and symptoms which led us to diagnose a massive pulmonary atelectasis. However, following bronchial aspiration and intravenous fluids and blood the patient rallied, and on the third post-operative day her temperature became normal. Thereafter during the remainder of her stay in the hospital the temperature never exceeded 99.8° F. rectally or 99° F. by mouth. She was sitting up in bed by the end of the first week and out of bed a few days later. Her entire disposition changed; she became a happy, euphoric patient who was the favorite of the ward. A blood culture taken 24 hours after operation was negative, as were repeated cultures taken at intervals during the three weeks after operation that she remained in the hospital.

Her blood count showed an increase in hemoglobin and red cells. The white blood count remained about the same. The systolic blood pressure remained about 120 mm. Hg, but the diastolic rose to 80 mm. During the short period of reaction after operation the electrocardiographic tracing was indicative of paroxysmal auricular tachycardia, but 10 days later was "within normal limits."

Auscultation immediately after suture of the wound showed that the loud "machinery" murmur had completely disappeared. The heart sounds remained normal in every way, and these auscultatory findings were confirmed by the cardiac sound tracing.

Thirteen weeks after operation the girl was apparently a normal healthy individual whose tolerance for exercise had increased over what it had been before her attack of endarteritis.

Note: At present, two years after the operation, the girl is well, healthy and to all appearances living a normal life.

BIBLIOGRAPHY

1. Gross, R. E., and Hubbard, J. P.: Surgical ligation of a patent ductus arteriosus, Jr. Am. Med. Assoc., 1939, cxii, 729.
2. Touroff, A. S. W., and Vesell, H.: Subacute streptococcus endarteritis complicating patent ductus arteriosus. Recovery following surgical treatment, Jr. Am. Med. Assoc., 1940, cxv, 1270.
Touroff, A. S. W.: A modified technique of surgical ligation of patent ductus arteriosus, Surgery, 1942, xii, 24.

TRICHINOSIS: A SPORADIC OUTBREAK WITH REPORT OF A CASE *

By James S. Sweeney, Col., MC, F.A.C.P., Frank B. Queen, Lt. Col., MC, and Thomas F. Barrett, Capt., MC, *Brigham City, Utah*

Trichinosis is a disease about which little is written at the present time, partly because it is infrequently diagnosed. We are inclined, as are others, to suspect that chronic trichinosis is much more prevalent in this country than might be indicated by the literature and statistics.

The purpose of this paper is to draw attention to this condition and to report a case observed in this hospital. The patient was one of many victims of a very severe outbreak which led to an unusually interesting epidemiologic study.

Case Report

Our patient, aged 32, was inducted into the Army September 5, 1942, at Butte, Montana. He never completed his basic training. He was assigned to the Medical Detachment at Bushnell General Hospital on September 25, 1942. He reported to sick call and was hospitalized in November 1942. His complaints were those of soreness in his back and legs for the preceding year and a half. He stated that these symptoms had grown progressively worse. Before induction into the Service he worked on a small farm. His mother was living at the age of 60 but was not well, being troubled with high blood pressure. His father had died in 1940 at the age of 63 of diabetes

* Received for publication November 13, 1943.
Bushnell General Hospital.

mellitus complicated by gangrene. He had nine brothers living, three of whom he stated, had complaints similar to his. He had seven sisters living, five of whom likewise had similar complaints. One brother had died on December 26, 1937, from meningitis (actually trichinosis.)

The past history of our patient was essentially negative except for an attack of influenza in 1919, typhoid fever at the age of 15, and an attack of severe diarrhea in 1937. His physical examination was likewise essentially negative. He was a well developed and healthy appearing individual. There was a definite spasticity of the left gastrocnemius muscle associated with tenderness in the proximal area of this muscle. There was subjective soreness in the right leg but no gross tenderness was elicited.

The patient's present illness began in the latter part of 1937. He stated that at this time, besides himself, others of his family and many friends became ill with similar symptoms. His illness followed the consumption of some home-cured sausage and ham, his symptoms appearing approximately 10 days after eating the hog meat. His trouble began with diarrhea, abdominal cramps, weakness and intermittent fever. About 10 days after the onset of these symptoms his eyes became swollen and, as he expressed it, he thought they were going to burst. There was an associated edema of his face. Three days later he developed severe pains all over his body, marked about his joints. These severe pains were intermittent in character and lasted for a period of approximately six weeks. There was some slight swelling of some of the joints at intervals. He also had considerable pain in his muscles of mastication and at times could hardly open his mouth. For a while he had to be fed with a tube. Throughout his acute illness there was profuse sweating.

The other members of the family had similar symptoms varying in degree and intensity. In addition to the symptoms the patient described, he stated that some of his brothers complained of severe itching and shortness of breath during the acute phase of their illness. Our patient was hospitalized during his illness for a period of 40 days and was discharged only to have a relapse and be readmitted, remaining the second time for a period of five weeks. Since his last discharge, he had felt only fairly well and his work had been limited to light farming. He stated that when he stood on his feet over a long period of time, the calves of his legs and back ached severely.

At the time the patient was observed in this hospital, all of the laboratory findings were essentially negative including the blood count, in which there was no increase of eosinophiles. Skin tests for trichinosis were also negative. Roentgenographic plates of his legs were negative. Because of the excellent history presented by this patient, it was felt that in all probability he had a trichinal infestation. A piece of muscle was, therefore, removed from his left leg for biopsy. Sections of the muscle studied at the National Museum revealed the larvae of trichina ranging from 570 to 640 cysts in 0.28 gm. of muscle. There was a total of 41 such cysts showing calcification and degeneration (these did not show in the roentgenograms).

As a result of these findings inquiry was made as to the other individuals afflicted from the same exposure experienced by our patient. We found through the Montana Health Department and other sources that in the Fall of 1937, our patient's family moved from North Dakota to Columbia Falls, Montana. They carried with them 12 of their pigs, and on their journey picked up 11 more in Eastern Montana. About the middle of October 1937, they began to kill their hogs for the purpose of securing their meat for the winter. They cured some of the hams and also made sausage. According to information obtained from Dr. H. F. Wilkins, Chief Deputy State Veterinarian of Montana, the products from the first three hogs killed between October 15 and November 10 were rather promptly consumed by the patient's family. These products were fried, roasted and boiled and there is some doubt as to whether

these hogs were infested with trichina, as they were fed separately from the others. On November 16 six more hogs were butchered, among which was a large stag. It is definitely known that the stag was heavily infested and that his meat constituted a large portion of that used in making smoked sausage. The sausage was put up in casings, smoked one day, rested one day, and then smoked three days, after which the family began eating it.

A party was held at the patient's home on December 14 and since no other hogs were killed until December 29, it seems that the six hogs just referred to above were the main offenders as far as the infested products were concerned.

It is reasonable to assume that the members of the household acquired their infestations some time following November 20 and during the early part of December, prior to the party of December 14. Details of sausage consumption by the family during this interim are not available. It is known, however, that the infested meat was eaten intermittently following its preparation which was completed on or about November 19 or 20. The exact incubation period, therefore, is difficult to establish in individual cases.

In one instance, namely, that of the 11 year old brother of our patient, there is some tangible evidence as to the incubation period. We are informed that on November 29 this youngster ate a large quantity of the smoked sausage. On December 2, he presented symptoms of excruciating abdominal pain, profuse vomiting, diarrhea and sweating. It is highly probable that this lad, as well as some of the rest of the family, had eaten some of the sausage prior to November 29, since the meat was ready for consumption on or about November 19 or 20. If this be true and our evidence is very strong that it is, it may be stated that the incubation period varied from three days to two weeks. Following the party on December 14, in a number of cases symptoms first appeared three, four, and five days later, up to and including two weeks, among those who were exposed at this time.

The laboratory findings in these cases are of interest, although they are incomplete. Of the 38 cases, there are records of eosinophile counts in 28. The percentage of eosinophiles varied from 0 to 70 per cent. The highest count of 70 per cent was that of the younger brother of our patient, who died from his infestation. The average of the eosinophile counts of those checked was 21 per cent. There were 23 skin tests done on the 38 patients of which 17 were positive and six were doubtful.

It is of interest to review in a little more detail some of the symptoms of the group infested and describe especially the course of the illness in the younger brother which terminated fatally. The symptoms in the order of their appearance were vomiting, diarrhea (5 to 20 pea soup stools per day without blood), griping abdominal pains, headache, severe pains across the back, puffiness about the eyelids and face, varying degree of photophobia, extreme soreness in the muscles of the arms and legs, and marked prostration with sweating in about 30 per cent of the cases. Approximately 15 per cent of the victims complained of intense itching. The temperature varied up to as high as 105° F.

The one fatal case was the 11 year old brother of our patient, just referred to above. He ate an unusually large quantity of home-cured sausage on November 29 and his symptoms began on December 2. There was a diminution of the intensity of his symptoms in a few days and the boy continued to eat the sausage when he felt like eating. On December 16, his condition grew worse and he was taken to the hospital with a recurrence of all the manifestations mentioned above in an exaggerated form. In addition he showed signs of meningeal irritation. A spinal puncture was done and live trichinae were found in the spinal fluid. After a very stormy course, the boy died on December 26, 10 days after his admission to the hospital.

There were several who were present in the gathering who did not eat any of

TABLE I

Case No.	Sex	Age	Date of Onset
1	M	15	November 22, 1937
2	M	27	November 24, 1937
3	M	30	November 23, 1937
4	M	21	November 28, 1937
5	M	11	December 3, 1937
6	M	32	December 3, 1937
7	F	16	December 5, 1937
8	M	13	December 5, 1937
9	F	29	December 5, 1937
10	M	3	December 5, 1937
11	M	31	December 6, 1937
12	F	19	December 7, 1937
13	M	29	December 7, 1937
14	F	9	December 7, 1937
15	F	41	December 8, 1937
16	F	55	December 9, 1937
17	M	25	December 9, 1937
18	M	20	December 9, 1937
19	M	44	December 12, 1937
Guests at Party 14 December 1937			
20	M	35	December 17, 1937
21	F	28	December 17, 1937
22	M	36	December 17, 1937
23	F	40	December 18, 1937
24	F	28	December 20, 1937
25	M	18	December 20, 1937
26	M	10	December 22, 1937
27	M	49	December 23, 1937
28	F	31	December 23, 1937
29	F	54	December 23, 1937
30	M	20	December 23, 1937
31	M	31	December 23, 1937
32	M	36	December 24, 1937
33	M		December 25, 1937
34	M	23	December 26, 1937
35	M	8	December 27, 1937
36	M	6	December 27, 1937
37	M	49	December 28, 1937
38	F	19	January 3, 1938

the hog meat and who, of course, showed no signs of illness. One family took some of the meat home with them but ate none of it at the party. Later they cooked it thoroughly and consumed it without any ill effects. In table 1 is a list of the cases, their age, sex, and date of onset of symptoms. These data have been provided by the Montana Health Department, local health service and the family physicians.

This interesting sporadic outbreak of trichinosis should be a warning to all the medical profession and health agencies. Those of us in the military hospitals should be on the alert for the recognition of trichinosis in cases of ill defined aches and pains and cases of unexplained eosinophilia. We are reminded, too, that frank symptoms of trichinosis may be present over a surprisingly long period of time—in our case for five years. It is not clearly understood just how long these parasites may remain viable in the human host. An investigation made on July 8, 1938, revealed that all the adults involved in this epidemic had residual symptoms of muscle soreness and at times acute muscle cramps in their legs. The residual symptoms were not so marked in children as in the adults. The adults were able to do some work, though they tired very easily and it was estimated that they were able to attend to from one quarter to one half of all their normal duties.

It is generally agreed that the severity of symptoms is proportional to the number of cysts ingested, as was so cogently demonstrated by the younger brother who continued to eat the infested sausage; also upon reinfestation because there is no immunity established as a result of one infestation. It should be remembered, finally, that other animals besides hogs may be carriers of the trichina, namely rats and bears. There is no known treatment for the state of encystment. The treatment during the acute phase or period of invasion is thorough catharsis supplemented with vermifuges. The most effective treatment is the prophylactic approach which involves simply thorough cooking of pork and sausages.

DERMATITIS DUE TO BARBITURATES: REPORT OF A CASE WITH ASSOCIATED ANEMIA *

By J. K. Potter, M.D., and R. J. Whitacre, M.D.,
East Cleveland, Ohio

The widespread use of barbiturates has resulted in numerous reports of reactions following their use. The type of reactions following ordinary doses of barbiturate is usually a form of dermatitis. Phenobarbital was introduced to the medical profession in 1911. A few months later Loewe [1] reported the first cutaneous reaction following the use of this drug. The skin manifestations were relatively mild and promptly disappeared upon withdrawal of the drug. Hamilton [2] reported the first case of universal exfoliative dermatitis due to phenobarbital in 1926. The majority of patients who have had skin reactions following the administration of barbiturates have recovered. However, fatal terminations have been reported. [3, 4, 5, 6]

* Received for publication April 16, 1943.

The pathologic lesions associated with cutaneous reactions due to barbituric acid derivatives have not been clearly defined. Schulte [7] was unable to detect microscopic changes in the tissues of animals which had been subjected to repeated doses of barbiturates. Winer and Baer, [6] in reporting a fatal case of exfoliative dermatitis due to phenobarbital, stated that the autopsy findings were similar to those produced in toxic reactions to arsphenamine. There was a cellular infiltration of the internal organs by eosinophiles. Sexton, Pike, and Nielson [5] reported a case of exfoliative dermatitis and death due to phenobarbital. At autopsy there were no significant findings other than a bronchial pneumonia which was probably the result of drug depression. The following is a case report of dermatitis due to barbiturates associated with anemia.

Case Report

On October 19 a white female, aged 46, in good physical condition, was admitted to the hospital for a thyroidectomy. The patient was receiving Lugol's solution, 15 minims three times a day, preoperatively. Temperature and respirations were normal, pulse 120, blood pressure 170 mm. Hg systolic and 98 mm. diastolic, basal metabolic rate + 28 per cent, hemoglobin 92 per cent, and red blood count 4,350,000. The white blood cell count was 7,500, with polymorphonuclears 76 per cent and lymphocytes 24 per cent. Repeated white blood cell counts during the patient's stay in the hospital did not reveal any material change. On October 20 luminal gr. 1½ (0.1 gm.) was given at 10:00 a.m. At 1:30 p.m. she had a chill followed by a rise in temperature which reached a maximum of 104° F. at 4:00 p.m. During this time a marked erythema developed over the entire body. On October 21 luminal gr. 1½ (0.1 gm.) was repeated at 12:00 m. Following this, the patient had a severe chill and by 4:00 p.m. the temperature was 103.8° F. At this time the erythema was even more pronounced and caused the patient considerable discomfort. Luminal and iodine medication was discontinued. Being unable to sleep the patient on October 22 at 1:30 a.m. was given amytal gr. 1½ (0.1 gm.) and aminopyrine gr. 3½ (0.23 gm.). This was followed promptly by a severe chill and the temperature was elevated to 103.6° F. by 2:30 a.m. At 8:00 a.m. the patient's temperature, pulse and respirations were normal, but her entire body was covered with large serous filled blebs. On this date the hemoglobin was reduced to 80 per cent and the red blood cells to 3,900,000. During the next few days the patient was very uncomfortable owing to the skin eruptions. The patient became progressively more anemic until October 29 when the hemoglobin was 58 per cent and the red blood count 3,000,000. At this time there were large indurated areas over the entire body and desquamation had started. Following this the general condition of the patient improved sufficiently for a thyroidectomy to be done. There were no further complications. Roth [8] has reported the occurrence of mild hyperchromic anemia in cases of exfoliative dermatitis due to barbiturates, but apparently anemia is an unusual complication.

The increased use of barbiturates as preoperative sedatives and as anesthetic agents makes it desirable to be aware of the relative frequency with which these reactions occur. Menninger,[9] in 1928, could find only 41 reported cases of cutaneous eruptions due to barbiturates. Since that time the number of cases reported in the literature has steadily increased. Many authors [4, 9, 10, 11, 12, 13] believe that from 1 to 3 per cent of patients taking phenobarbital will show a toxic skin rash. Cutaneous reactions apparently occur following all types of barbiturates. However, the long-acting barbiturates such as phenobarbital

(luminal) cause skin reactions more frequently than the short-acting barbiturates such as pentobarbital sodium (nembutal) or sodium propyl-methyl-carbinyl allyl barbiturate (seconal). Dietrich [14] has not observed cutaneous reactions in 3,700 cases in which seconal was used. In the last 10,000 recorded cases in which pentobarbital sodium was used we have not noted a single skin manifestation. The ultra short-acting barbiturates as pentothal sodium and evipal have been used extensively to produce surgical anesthesia but like the short-acting group they have rarely caused skin eruptions. This is significant to the surgeon and anesthetist because their use of barbituric acid derivatives is limited for the most part to the short-acting and ultra short-acting groups.

Various types of cutaneous reactions have been reported. The urticarial type in which wheals or angioneurotic edema occurs is the most common form. The onset occurs promptly and rapidly disappears upon discontinuing the drug. The erythematous type may become diffuse and go on to an exfoliative dermatitis. In other cases, vesicles, large blebs, or bullae occur which may become necrotic. Novy [15] described a fixed type of eruption which is characterized by recurrences of the skin manifestation in exactly the same location of the body. In these cases the involved area often becomes pigmented. Stryker [16] reported a case of erythematous dermatitis with red, swollen, exfoliative skin, stupor and rise of temperature due to a barbiturate which was followed by photo-sensitization of the skin. On exposure to sunlight four months later there was a reappearance of the dermatitis. Moss and Long [17] reported two cases that had in addition to the skin eruption involvement of all mucous surfaces except those of the bronchial and urinary system. No obvious loss of hair occurred, but each eventually shed all his finger nails and toenails. It has been noted [4, 17] that in certain cases an exudate may occur in the pharynx causing a pseudo-membrane suggesting diphtheria.

The dose of barbiturate is not an important factor, since very small quantities will produce skin eruptions in sensitive individuals. [15] Skin reactions may follow the administration of a single dose of barbiturate. However, it is believed [18] that these reactions occur more frequently after the repeated use of barbiturates, indicating that sensitization may be acquired. It has been suggested [19] that nearly all drug eruptions are in this category of acquired sensitization. At the present time there are no satisfactory tests to determine whether a patient is sensitive to barbiturates other than by clinical trial. The patch test and skin wheal are unreliable as methods of determining a patient's sensitivity.[20, 15, 17] It has been noted that patients who show intolerance to one barbiturate are often sensitive to other barbituric acid derivatives.

Summary

A case of exfoliative dermatitis associated with anemia due to barbiturates is reported. Although barbiturates are very widely used it is not generally realized that certain groups of barbituric acid derivatives cause skin reactions in 1 to 3 per cent of the cases in which they are used. Occasionally these reactions terminate fatally. The skin eruptions usually occur with ordinary doses of the drug. In some instances repeated doses of a barbiturate increase the patient's sensitivity. In such cases dermatitis occurs after the continued use of the drug.

The long-acting barbiturates, such as phenobarbital, cause the greatest number of cutaneous reactions. The short-acting barbiturates, such as pentobarbital sodium, and the ultra short-acting barbiturates, such as pentothal sodium, rarely precipitate skin reactions.

BIBLIOGRAPHY

1. Loewe, S.: Klinische Erfahrungen mit Luminal, Deutsch. med. Wchnschr., 1912, xlii, 947.
2. Hamilton, E. S., Geiger, C. W., and Roth, J. H.: Luminal poisoning with conjunctival residue, Illinois Med. Jr., 1926, xlix, 344.
3. Chavany, J. A., and Vannier, P. E.: Toxidermie barbiturique à type d'érythème scarlatiniforme infiltré, Progrès Méd., 1929, xliv, 1685.
4. Wile, U. J., and Benson, J. A.: Exfoliative dermatitis due to phenobarbital with fatal outcome: report of 2 cases, Ann. Int. Med., 1940, xiii, 1243.
5. Sexton, D. L., Pike, G. M., and Nielson, A.: Exfoliative dermatitis and death due to phenobarbital, Jr. Am. Med. Assoc., 1941, cxvi, 700.
6. Winer, N. J., and Baer, R. L.: Exfoliative dermatitis due to phenobarbital, Arch. Dermat. and Syph., 1941, xliii, 473.
7. Schulte, T. L.: Tissue changes in chronic intoxication of barbital, California and West. Med., 1939, 1, 256.
8. Roth, G. B.: The barbiturates and some of their side-effects, Med. Ann. Dist. Columbia, 1942, xi, 254.
9. Menninger, W. C.: Skin eruptions with phenobarbital (luminal), Jr. Am. Med. Assoc., 1928, xci, 14.
10. Scarlett, E. P., and Macnab, D. S.: Poisoning from phenobarbital (luminal), Canad. Med. Assoc. Jr., 1935, xxxiii, 635.
11. Poole, A. K.: Drug reactions from barbital (veronal) and phenobarbital (luminal), Yale Jr. Biol. and Med., 1929, i, 345.
12. Huddleston, J. H.: Non-dermatological disturbances during continued treatment with phenobarbital, Jr. Am. Med. Assoc., 1929, xciii, 1637.
13. Taylor, H. W., and Schram, M.: Phenobarbital poisoning, Arch. Pediat., 1936, liii, 670.
14. Dietrich, Harry F.: Sodium propyl-methyl-carbinyl allyl barbiturate (seconal) as a sedative for infants and children: A clinical evaluation of one of the newer barbiturates, Anes. and Analg., 1943, xxii, 28.
15. Novy, F. G.: Drug eruptions due to the barbiturates, California and West. Med., 1938, xlviii, 324.
16. Stryker, G. V.: Barbituric acid dermatitis with photosensitization, Jr. Med., 1940, xx, 516.
17. Moss, R. E., and Long, W. E.: Toxic eruptions due to phenobarbital: report of two cases, Arch. Dermat. and Syph., 1942, xlvi, 386.
18. Bethea, O. W.: The barbituric acid salts, Internat. Med. Digest, 1932, xxi, 371.
19. Wise, F., and Sulzberger, M.: Drug eruptions: I. Fixed phenolphthalein eruptions, Arch. Dermat. and Syph., 1933, xxvii, 549.
20. Hill, B. P.: Hypersusceptibility to basal anesthetics, Brit. Med. Jr., 1938, ii, 1199.

SICKLE CELL ANEMIA SIMULATING CORONARY OCCLUSION *

By S. L. ZIMMERMAN, M.D., Major, M.C., A.U.S., and ROY BARNETT, M.D., Major, M.C., A.U.S., *Columbia, South Carolina*

INTRODUCTION

REAL and fancied cardiac disease in sickle cell anemia has been the subject of considerable discussion.[1, 2, 3, 4] Particularly has there been confusion with rheumatic fever, as dyspnea, palpitation, cardiac enlargement, systolic and diastolic apical murmurs, and prolonged P-R intervals are associated with arthralgias and fever in both diseases. Klinefelter [5] has recently dispelled the confusion. He found cardiac hypertrophy without valvular or endocardial abnormalities, or myocardial damage in all 11 of his autopsied cases of sickle cell anemia. This may be compared with entirely similar findings in 22 of 23 cases of pernicious anemia reported by Cabot.[6] In both anemias the hypertrophy is secondary to the anemia, although the exact mechanism is still uncertain.[7] The clinical symptoms and signs reflect the hypertrophy and dilatation.

Severe anemias of any type may become manifest as functional coronary insufficiency, although there is some doubt whether this can occur in an otherwise normal heart.[8] A preëxisting coronary sclerosis is usually necessary to produce symptoms or electrocardiographic changes.[8, 9]

In our case the hemolytic crisis of sickle cell anemia was accompanied by typical clinical features and suggestive electrocardiographic changes of coronary occlusion.

CASE REPORT

Patient L. J., a 30 year old colored male, was apparently well until June 1941, at which time, while carrying a bucket of coal, he was taken with a severe sense of substernal pain which radiated to both arms and was accompanied by profuse perspiration, nausea, and vomiting. He was hospitalized in the military service from June 10 to July 31, 1941. He denied syphilis, rheumatic fever, or other relevant illnesses. The family history was noncontributory.

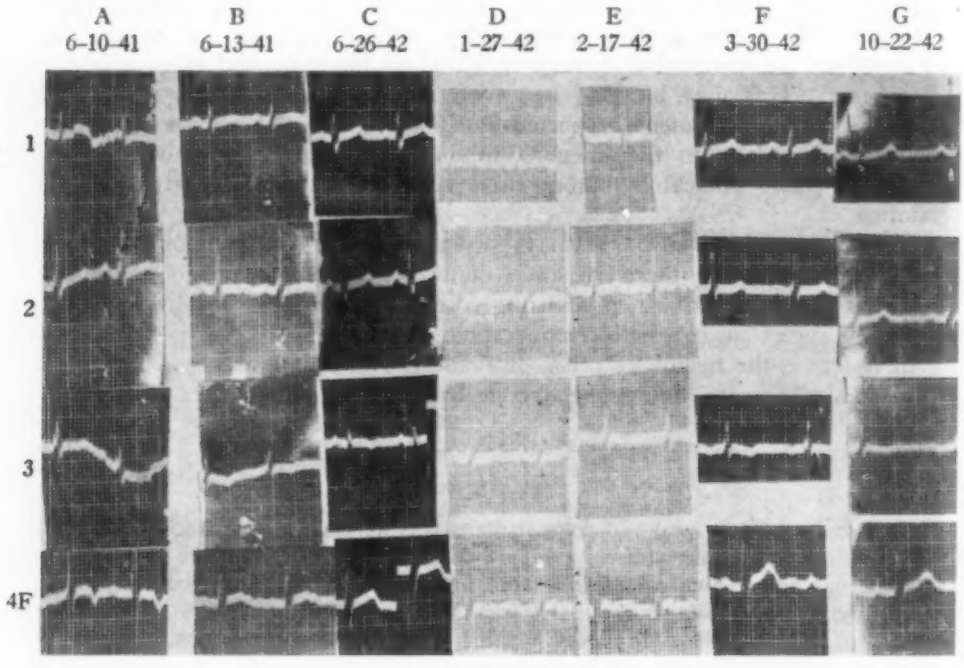
On admission the temperature was subnormal, the blood pressure 110 mm. Hg systolic and 80 mm. diastolic. The heart was slightly enlarged to the left, and there was a soft blowing apical systolic murmur present. A tentative diagnosis of coronary occlusion was made. Admission electrocardiogram (A) on June 10, 1941, revealed an inverted T-wave in Lead IV–F and broad and low T-waves in Leads I and II. There were no significant ST deviations, although the tracing was not entirely satisfactory.

He soon became febrile and icteric. Blood count on June 13, 1941 revealed red blood cells 2.8 million, white blood cells 11,800, polymorphonuclears 89 per cent, and lymphocytes 11 per cent. On the smear there was marked achromia, anisocytosis,

* Received for publication May 3, 1943.
From Cardiovascular Service, U. S. Veterans Administration, Columbia, South Carolina.
Published with the permission of the Medical Director of the Veterans Administration who assumes no responsibility for the opinions expressed or the conclusions drawn by the authors.

and poikilocytosis. Many sickle cells were reported. The Kahn reaction was negative. The urine was not remarkable. The icteric index was 36. On June 19, 1941 the red blood cells numbered 2.0 million. Many sickled forms were noted. The patient was placed on intramuscular liver extract, treated symptomatically and discharged July 31, 1941, improved, although available laboratory data recorded a final red blood cell count of 2.62 million with 50 per cent hemoglobin.

On the second electrocardiogram (B) taken three days after admission, the T-wave in IV–F was M-shaped and the T-wave in Lead II diphasic, but no ST deviations were apparent. There was moderate slurring of QRS in all leads. The third electrocardiogram (C) taken June 26, 1941, revealed a normally upright T–4 and increase in amplitude of the upright T-wave in Leads I and II. There was a



tendency toward right axis shift. At this time there was no longer any clinical evidence of a hemolytic crisis and the patient was asymptomatic.

The electrocardiographic changes described above were atypical in that they followed no particular pattern; however, they were not unlike those occasionally seen in anterior wall occlusions. They differed in that they occurred early and were unaccompanied by abnormal Q-waves or ST deviations. They reverted in a relatively short period of time.

The patient was readmitted November 7, 1941, for treatment of an acute nonsuppurative lymphadenitis. At that time there was no evidence of an acute hemolytic crisis, although a marked anemia and sickling were present. The red blood cells averaged 2.5 million and the hemoglobin ranged between 50 and 70 per cent, by the Talquist method.

On January 27, 1942, he was readmitted, acutely ill, again complaining of severe chest pain, headache, nausea, vomiting, and prostration. He had been relatively well in the interim. The heart was large, the area of precordial dullness

extending to the anterior axillary line. There was a blowing systolic apical murmur. There was no evidence of congestive failure. The blood pressure was 120 mm. Hg systolic and 70 mm. diastolic. The temperature reached a level of 102° F., but soon subsided. The pain persisted for a day or so and then subsided also. Blood studies again revealed the patient to be in an acute hemolytic crisis. There were electrocardiographic changes similar to those described above, namely, a small, broad T–1 and a notching of T–4 (IV–F). The final blood count of March 16, 1942, revealed a red blood cell count of 3.53 million with 70 per cent hemoglobin. The patient was subsequently transferred to a general hospital for disposition. Electrocardiogram F was taken while in remission, at which time his red blood cell count was 3.84 million and hemoglobin 75 per cent. Sickling remained present on all preparations, and the patient was discharged from the military service on March 21, 1942.

He was admitted to the Veterans Administration Facility, Columbia, South Carolina, October 22, 1942, at which time he was relatively asymptomatic. He was seen by the cardiologist, and the examination is quoted in full:

> "Examination reveals a 30 year old colored male who is ambulant, minimally dyspneic at rest, with no distention of the cervical veins in the erect position. In the recumbent position it is seen that the cervical veins distend and pulsate very slightly but this is probably a transmitted pulsation. Trachea is midline, there is no tug. Thyroid is not enlarged. Apical impulse is rather forceful. The point of maximum intensity is felt in the fifth intercostal space outside the midclavicular line. The left border agrees to percussion. There is no demonstrable clinical enlargement to the right to percussion and there is no increase in retromanubrial dullness. Rhythm is regular. The first sound over the mitral area is not snapping, and is followed by a blowing apical systolic murmur. In the recumbent position and left lateral prone position, there is no essential change heard in the murmur described above. There is heard over the pulmonic area a systolic murmur as well."

The exercise tolerance was within normal limits. There was no evidence of congestive failure. The radial vessels were thickened, but there was no evidence of retinal sclerosis. Roentgenographic examination of the chest revealed cardiac en-

Laboratory Data for Admission October 22, 1942

October 22, 1942	Icterus index 20.
October 22, 1942	Wassermann: Positive 100 per cent. Kahn: 4-plus.
October 23, 1942	Urinalysis: Yellow, acid, sp. gr. 1.008. Mucus, occasional shred, 3–4 per high power field. Epithelia, few squamous and round, remainder negative.
October 22, 1942	Urinalysis: Amber, acid, sp. gr. 1.015. Mucus, few shreds. W.B.C., occasional. Epithelia, few squamous. Remainder negative.
October 22, 1942	Blood cell: Erythrocytes, 2,120,000. Hemoglobin, 7.1 grams, 45 per cent, Newcomer. Cell volume 46 per cent. Volume index 1.09. Red cells show definite sickling.
October 27, 1942	Blood count: Erythrocytes, 2,120,000. Leukocytes, 8,900. Blood platelets, 311,640. Differential leukocyte: polys, 46–43 seg, 3 staff. Lymphocytes, 54. Monos, none. Eosinophiles, none. Basophiles, none. Hemoglobin 7.3 grams, 45.2 per cent, Newcomer. Color index 1.07. Polychromatophilia present. Anisocytosis present. Poikilocytosis present. No myelocytes found. Reticulocytes, 9.2 per cent. Nucleated reds, none seen. Red cells show definite sickling.
November 5, 1942	Sedimentation index, 2 mm. per hour.
November 6, 1942	Gastric analysis: Amount obtained, 60 c.c. Total acidity, 50. Free HCl, 35.
November 12, 1942	Total erythrocyte count, 2,920,000. Leukocytes, 15,600. Polys, 52. Lymphocytes, 48. Hemoglobin, 9.0 grams, 56.7 per cent.

largement, the measurements being: M. R., 5.3 cm.; M. L., 11.3 cm.; Chest 30.6 cm. Fluoroscopy in the lateral and right oblique position revealed a uniform enlargement of the heart, but no evidence of unusual left auricular predominance was noted. There was no encroachment upon the esophagus. Roentgenographic examination of the skull revealed serrations in the vertex of the calvarium.

The patient remained afebrile, but laboratory work-up revealed a moderate to marked anemia with evidence of blood destruction and regeneration. The icteric index was elevated. Sickling was persistently present. The detailed laboratory data are given below. Interestingly enough the Wassermann and Kahn reactions became positive. Electrocardiogram G was within normal limits. With antisyphilitic therapy, iron and liver, and a high caloric diet, he was discharged with a final red blood cell count of 3.05 million and a hemoglobin of 7.6 grams, 47 per cent, Newcomer method.

A final diagnosis of heart disease, due to sickle cell anemia with cardiac enlargement and myocardial damage, was made.

Discussion

Though minor electrocardiographic abnormalities, consisting of PR prolongation and variations in the amplitude of the T-wave, have been noted previously,[5, 10] we have not discovered T-wave reversal or changes of this magnitude in other reported cases. In the present instance the progressive reversible T-wave changes increased the original suspicion of coronary occlusion based on the clinical symptomatology.

There seems ample evidence that this is an instance of acute coronary insufficiency. It is very doubtful that any organic coronary artery disease exists, in view of the patient's age (30), race (negro), and the early return of the electrocardiogram to normal. Furthermore, the anemia per se could not have been the cause of the episodes described, as there was no change in red cell count during the recovery period. The necessary factor in the production of the coronary insufficiency was the hemolytic crisis. It is not possible to ascertain the exact mechanism, whether a sudden fall in red blood cells causing a sudden anoxemia, later compensated, or a toxic end product of red cell autolysis, or the same factor which induces the crisis itself.

Conclusion

A case of sickle cell anemia is reported in which the hemolytic crisis simulated a coronary occlusion clinically and to a lesser degree cardiographically.

BIBLIOGRAPHY

1. Anderson, W. W., and Ware, R. L.: Sickle cell anemia, Am. Jr. Dis. Child., 1932, xliv, 1055.
2. Anderson, W. W., and Ware, R. L.: Sickle cell anemia, Jr. Am. Med. Assoc., 1932, xcix, 902.
3. Graham, G. S.: A case of sickle cell anemia with necropsy, Arch. Int. Med., 1924, xxxiv, 778.
4. Sydenstriker, V. P., Mulherin, W. A., and Houseal, R. W.: Sickle cell anemia; report of two cases in children, with necropsy in one case, Am. Jr. Dis. Child., 1923, xxvi, 132.
5. Klinefelter, Harry F.: The heart in sickle cell anemia, Am. Jr. Med. Sci., 1942, cciii, 34.

6. Cabot, H. C.: Facts on the heart, 1926, W. B. Saunders, Philadelphia and London.
7. Fishberg, Arthur M.: Heart failure, 1940, Lea and Febiger, Philadelphia.
8. Katz, Louis N.: Clinical aspects of the electrocardiogram, 1941, Paul B. Hoeber, Inc., New York.
9. Pardee, Harold E. B.: Electrocardiography, 1941, Lea and Febiger, Philadelphia.
10. King, J. T., and Janeway, C. W.: Sickle cell anemia with cardiac complications, Internat. Clin., 1937, iii, 41.
11. Porter, W. B.: Heart changes and physiologic adjustment in hookworm anemia, Am. Heart Jr., 1937, xiii, 550.

EDITORIAL

CUSHING'S SYNDROME

SINCE Cushing's original description [1] of this symptom complex, the condition has become widely known, doubtless because of the striking and unusual symptoms it presents, in spite of its relative rarity. Cushing attributed the syndrome to a basophilic adenoma of the anterior lobe of the pituitary because this lesion was found in several of the 12 cases he collected. Following his report the syndrome was widely regarded as a manifestation of hyperpituitarism.

Subsequent observations, however, have cast serious doubt on this conclusion. There is no constant relationship between the occurrence of basophilic adenomata and the symptom complex. Many patients with basophilic adenomata have been reported who did not show these symptoms. Conversely, many clinically typical cases of the syndrome have shown no pituitary adenoma, but often a tumor or other significant lesion elsewhere, most frequently in the adrenal cortex, or more rarely in the thymus.

Moreover, a critical survey of the principal symptoms reveals that many of them suggest a deficiency rather than an overactivity of the pituitary. Among the most prominent features may be mentioned the obesity, often painful, commonly described as the "buffalo" type, affecting especially the face, neck, the trunk and markedly the abdomen, and sparing the limbs. Cutaneous changes are marked and include hypertrichosis, dryness and fragility of the skin with marked acne and susceptibility to superficial infections, a dusky flushing which may be associated with an actual polycythemia, and the characteristic purplish atrophic striae on the abdomen and thighs. Occasionally there may be a cutis marmorata, ecchymoses, or brownish pigmentation.

There is usually hypertension and more or less marked generalized arteriosclerosis. There is progressive weakness and prostration, with pains in the back, limbs and abdomen.

There is usually a kyphosis of the dorsal spine, accentuating the buffalo appearance. There is also in most cases a general reduction in the density of the bones, an osteoporosis which may become extreme and lead to pathological fractures, including compression fractures of the vertebral bodies. The pathogenesis of this change is still in doubt, but there is no convincing evidence that it is due to hyperparathyroidism.

Eventually there is usually evidence of depressed thyroid activity, as shown by a reduced basal metabolic rate and a high blood cholesterol. Gonadal activity is also depressed as indicated by amenorrhea, loss of libido and arrest of normal development of ovarian follicles in females and cor-

[1] CUSHING, HARVEY: Papers relating to the pituitary body, hypothalamus and parasympathetic nervous system, 1932, Charles C. Thomas, Springfield, Ill.

responding disturbances in males. Less constantly but frequently there is a disturbance of carbohydrate metabolism with hyperglycemia and glycosuria. There may also be a disturbance of water balance with polyuria and polydipsia.

These varied symptoms indicate a marked and wide spread endocrine disturbance and suggest a general depression of function (except for the adrenal cortex) which may in considerable measure be a direct or indirect result of a deficiency of hypophyseal secretion. The adrenal cortex, on the other hand, appears in many cases to be hyperactive. In a substantial portion of the cases of Cushing's syndrome there have been found either cortical tumors or a well marked diffuse hyperplasia of the cortex. Removal of such a tumor has been followed by a remission of symptoms.[2] However, such adrenal lesions have been demonstrated in only a portion of the cases, and no single gross lesion has been found constantly present in all cases.

In 1935 Crooke [3] reported a study of 12 cases of Cushing's syndrome in all of which he found a hyalinization of the cytoplasm of the basophilic cells of the hypophysis which he interpreted not as a degenerative or necrobiotic change but as an indication of a physiological disturbance which he thought might furnish a basis for the development of Cushing's syndrome. Of these 12 cases, 6 showed a basophilic adenoma of the pituitary, three a tumor of the adrenal cortex, and three a tumor of the thymus. This hyalinization was not present in appreciable degree in a large number of control cases, including cases of acidophilic and basophilic cell adenomata of the pituitary which did not show the Cushing syndrome clinically. Crooke's observations as to the hyaline change in the basophilic cells in Cushing's syndrome have been confirmed by Rasmussen [4] in three cases and by Heinbecker [5] in five cases. The exact significance of this hyalinization is not yet clear, however, nor has any single cause for its development been found.

As accumulating evidence tended to discredit the significance of basophilic adenomata as a cause of Cushing's syndrome, interest has centered increasingly on the adrenal cortex. As has been noted, cortical tumors and diffuse hyperplasia of the adrenal cortex constitute the most frequent potentially significant lesions found in these cases. Among others, Albright and his associates [6] have supported the view that the syndrome is the result of "hyperadrenocorticism." It has not been possible clinically to differentiate

[2] Ravid, Jacob M.: Cortical carcinoma of the adrenal with adrenogenital syndrome associated with an adenoma of the pituitary, Am. Jr. Path., 1935, xviii, 764.

[3] Crooke, A. C.: Change in basophile cells of pituitary gland common to conditions which exhibit syndrome attributed to basophile adenoma, Jr. Path. and Bact., 1935, xli, 339–349.

[4] Rasmussen, A. T.: Relation of basophilic cells of human hypophysis to blood pressure, Endocrinology, 1936, xx, 673–678.

[5] Heinbecker, P.: The pathogenesis of Cushing's syndrome, Medicine, 1944, xxiii, 225–247.

[6] Albright, F., Parson, W., and Bloomberg, E.: Cushing's syndrome interpreted as hyperadrenocorticism leading to hypergluconeogenesis; results of treatment with testosterone propionate, Jr. Clin. Endocrinol., 1941, i, 375–384.

cases with adrenal cortical lesions from cases without them with any certainty.

Recent observations of Heinbecker [5] appear to throw light on some of the cases of Cushing's syndrome which do not have adrenal lesions. By the experimental production of destructive lesions in the hypothalamus he was able to produce in dogs a condition showing some of the features of Cushing's syndrome in man. The animals became obese and showed diabetes insipidus. They showed changes in the thyroid, gonads and (in some individual animals) in the pancreas which were interpreted as regressive and indicating depression of function. The adrenals were normal. There was a loss of granulations in the basophilic cells of the anterior lobe of the pituitary, although the hyalinization seen in human cases was not exactly duplicated. These animals were abnormally sensitive to the administration of adrenal cortical hormone.

He also made a careful study of this portion of the brain in five human cases of Cushing's syndrome. In one case which showed an adrenal tumor, no abnormalities were found in the hypothalamus. In all the other four cases which showed normal adrenals he found a marked degree of atrophy of the nerve cells in the hypothalamic nuclei. In two of the cases a small basophilic adenoma of the anterior pituitary was noted, but not in the others. All cases, however, showed the hyalinization of the basophilic cells described by Crooke. This Heinbecker also regards as the significant lesion common to all cases, and he believes it indicates a depression of function which results also in a secondary depression of the gonads and the thyroid. Basophilic adenomata, if present, he thinks are of secondary significance and suggests that they may indicate an attempt on the part of the anterior pituitary to compensate for decreased function of the basophilic cells. This hyalinization and depression of function of the basophilic cells may be due directly to pathological overactivity of the adrenal cortex or to a tumor of the thymus, or it may result from atrophy of the hypothalamic nuclei with an apparently normal adrenal function. Based on his animal experiments, Heinbecker suggests that the hypothalamic lesion may operate by increasing the sensitiveness of the hypophysis to cortical hormone, so that a normal cortical secretion may bring about the same changes in the basophilic cells that are caused by a hypersecretion in individuals with a normal hypothalamus.

There is not as yet sufficient evidence to decide these points, and a solution perhaps may wait until adequate methods are available for identifying and measuring the hormones presumably concerned. Meanwhile, in the present state of knowledge, the most promising therapeutic approach appears to be a search for a lesion in the adrenals (or thymus) rather than a direct attack on the pituitary, whether by surgical or roentgenological measures.

REVIEWS

Textbook of Gynecology. Second Edition. By EMIL NOVAK, M.D., F.A.C.S. 708 pages; 16.5 × 24 cm. 1944. Williams and Wilkins Company, Baltimore. Price, $8.00.

Although only three years have elapsed since the appearance of the first edition, this new volume of Dr. Novak's textbook is in many ways a new book.

The present treatment of the topic of generative embryology as a single chapter is a definite improvement. The collaboration of Dr. Meyers in this chapter makes the book of great value to specialists as well as students.

The addition of a chapter on female urology, by one of the outstanding men in this field, gives the student and general practitioner an insight into the close relationship between gynecological and urological conditions.

The text of the book continues to be a little lengthy and repetitious. The illustrations are more numerous but, as in the first edition, lack the simplicity which is so essential in presenting the problem of gynecology to students. However, both criticisms are minor ones, and in general the second edition deserves the same success as the first.

W. K. D.

X-Ray Examination of the Stomach. By FREDERIC E. TEMPLETON, M.D. 516 pages; 23.5 × 16 cm. 1944. University of Chicago Press, Chicago. Price, $10.00.

With the exception of lipiodol myelography, fluoroscopy is more vital in making a roentgen diagnosis in diseases of the gastrointestinal tract than any other phase of roentgenology. In preparing his volume of roentgen-ray diagnosis of the upper gastrointestinal tract, Dr. Frederic E. Templeton evidently had this belief in mind, for he repeatedly emphasizes the fluoroscopic appearance of lesions of the upper gastrointestinal tract, and his differential diagnoses are based largely on the findings made while the patient is being examined fluoroscopically.

The material of the book is divided into a section dealing with the spot filming fluoroscope and the technic of using this machine, and other sections discussing the diseases of the esophagus, stomach and duodenum. Since few doctors have a spot filming fluoroscope available, this portion of the book is of only passing interest. The other sections, though, are well worth careful perusal, for the descriptions of roentgenological evidence of diseases of the esophagus, stomach and duodenum are clear, concise and accurate. Profuse illustrations have been inserted throughout the text, and the only comment needed concerning these is that they are adequate in number and are excellent.

Throughout the book, there are frequent references to the patterns of the mucosa of the esophagus, stomach and duodenum. There is no doubt left in the reader's mind that the author considers the mucosal patterns to be of paramount importance in locating and differentiating the lesions in question. Numerous pages are devoted to describing in detail the normal and the abnormal mucosal patterns as seen by the author and others. Perhaps the greatest criticism that can be made of this book is the innumerable references to the works of other roentgenologists and gastroenterologists who, as is so common among doctors, have contradictory views about the mucosa of the gastrointestinal tract. If one is particularly interested in research as regards the roentgenographic appearance of the mucosa, then the numerous references will be of help, but to the average physician, this part of the book will be only confusing and tiresome.

The author's last chapter is perhaps his most useful one to the reader. Here, in a brief though complete summary, the various points of differential diagnosis of lesions of the upper gastrointestinal tract are enumerated and compared. Thus, the busy practitioner can quickly consult this chapter, to aid him in his work, without having to read through one of the more lengthy ones. If this text is found to be inconclusive on some particular subject, or if further reading is desired, the author has a very long list of references added; this bibliography contains the names of not only American writers, but many foreign ones.

The reviewer has no hesitancy in stating that this volume of Dr. Templeton's is worthy of reading, for the information to be gained far outweighs the effort required to read it. The selling price of $10 might be considered a little excessive for a book no larger than this one, but, like the references of the mucosal patterns, this is a debatable point.

D. J. B.

Gynecological and Obstetrical Urology. By HOUSTON S. EVERETT, A.B., A.M., M.D. 517 pages; 23.5 × 16 cm. 1944. Williams and Wilkins Company, Baltimore. Price, $6.00.

This book represents the first correlation of the specialties of gynecology and obstetrics with that of urology. The importance of the interrelationship of each can not be too fi.mly stressed, and is something that becomes more obvious as the text of Dr. Everett's book is carefully reviewed.

The author has had wide experience in this work, at both the Johns Hopkins and Maryland University Medical Schools. He has also had personal association with the outstanding authorities in these fields. In addition he has the rare faculty of intelligent interpretation and logical organization.

The book is one which the specialist will find an indispensable working guide to his urological problems. It is also the type of volume which becomes of increasing value to the general practitioner in this daily contact with women.

The chapter on cystoscopy sets forth simply and clearly the technic for the Kelly method of aeroscopic cystoscopy, and omits for the most part the finer details of the more familiar water method. This should prove itself of value to all those who have heard of this method, but until now have been unable to put it into practice for lack of an authoritative description of the technic. However, in all fairness to the method, it must not be assumed to be so simple as to require neither training nor experience, for without these cystoscopy by the Kelly method will lead only to confusion. The Kelly method is for many procedures unexcelled, but in others it is inferior to the water method. Training and judgment are needed to select the proper method for any individual case.

Dr. Everett's treatment of the topic of bladder inflammations is excellent, and he has here brought up to date the complicated picture of chemotherapy. Other sections equally well written are those of calculi and renal tuberculosis, both at best difficult to present.

The illustrations are all of good quality and clarity. The drawings by Malone, a student of the late Max Brodel, are entirely accurate and understandable. The views of the interior of the bladder made through the Kelly cystoscope may be confusing to those urologists accustomed only to the picture as seen through the water scope.

The criticisms of this review are made in a constructive sense, and in no way affect the opinion that Dr. Everett's book is to be the authority for urological problems in women.

W. K. D.

BOOKS RECEIVED

Books received during October are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

Surgery of the Hand. By STERLING BUNNELL, M.D. 734 pages; 26 × 19 cm. 1944. J. B. Lippincott Company, Philadelphia. Price, $12.00.

Proteins and Amino Acids—Physiology, Pathology, Therapeutics. 189 pages; 23 × 15 cm. 1944. The Arlington Chemical Company, Yonkers, New York.

The Diseases of the Endocrine Glands. By HERMANN ZONDEK, M.D. (Berlin). Fourth (Second English) Edition. Translated by CARL PRAUSNITZ GILES, M.D. (Breslau), M.R.C.S. (Eng.), L.R.C.P. (Lond.). 496 pages; 23.5 × 15.5 cm. 1944. Williams and Wilkins Company, Baltimore. Price, $11.00.

Ventures in Science of a Country Surgeon. By ARTHUR E. HERTZLER, M.D. 304 pages; 23.5 × 16.5 cm. 1944.

Gynecological and Obstetrical Urology. By HOUSTON S. EVERETT, A.B., A.M., M.D. 517 pages; 23.5 × 16 cm. 1944. Williams and Wilkins Company, Baltimore. Price, $6.00.

The Medical Clinics of North America. Boston Number. Twenty-two contributors. 263 pages; 23 × 15 cm. September, 1944. W. B. Saunders Company, Philadelphia. (Published bi-monthly—price per year, $12.00.)

Recent Advances in Anaesthesia and Analgesia (Including Oxygen Therapy). Fifth Edition. By C. LANGTON HEWER, M.B., B.S. (Lond.), D.A. (Eng.). 343 pages; 21 × 14 cm. 1944. The Blakiston Company, Philadelphia. Price, $5.50.

Physiology in Health and Disease. Fourth Edition, thoroughly revised. By CARL J. WIGGERS, M.D., D.Sc., F.A.C.P. 1174 pages; 24 × 16 cm. 1944. Lea & Febiger, Philadelphia. Price, $10.00.

Studies on Immunisation. Second Series. With appendices dealing with anti-typhoid inoculation, chemo-therapy, and statistical and other operations of induction. By SIR ALMROTH E. WRIGHT, M.D., F.R.S. 256 pages; 25.5 × 19.5 cm. 1944. William Heinemann, Medical Books, Ltd., London. Price, 25s net.

A Method of Anatomy—Descriptive and Deductive. Third Edition. By J. C. BOILEAU GRANT, M.C., M.B., Ch.B., F.R.C.S. (Edin.). 822 pages; 26 × 18 cm. 1944. Williams and Wilkins Company, Baltimore. Price, $6.00.

Diagnóstico Topográfico de los Procesos Pleuropulmonares. Estudio Anatómico, Clínico y Radiológico. By DR. JUAN SOTO BLANCO. (Colección de Monografías—Monografía No. 1.) 106 pages; 29 × 20.5 cm. 1944. Imprenta "Rosgal," de Hilario Rosillo, Montevideo, Uruguay.

Primera Conferencia Argentina, Buenos Aires, October of 1943. Relatos Oficiales. Contribuciones y Discusiones. 307 pages; 20 × 14 cm. 1943. Published under the direction of Dr. Santiago I. Nudelman, Secretary, Buenos Aires.

COLLEGE NEWS NOTES

Additional A. C. P. Members Enter the Armed Forces

Dr. J. Roscoe Miller, F.A.C.P., Chicago, Dr. Gustavus A. Peters (Associate), Rochester, Minn., and Dr. Harry A. Senekjie (Associate), New Orleans, have recently entered the Armed Forces, bringing the total number of members on active military duty to 1,720.

Lt. Comdr. James P. Jordan (Associate), (MC), USNR, of Buffalo, N. Y., died July 23, 1944.

New Life Members

The College is gratified to announce that the following Fellows of the College became Life Members during the month of November:

Dr. Thomas P. Murdock, Meriden, Conn.
Dr. Delivan A. MacGregor, Wheeling, W. Va.
Dr. Leon S. Gordon, Washington, D. C.

Gifts to the College Library

The following gifts of publications by members are gratefully acknowledged:

Reprints

Dr. A. J. Atkinson (Associate), Chicago, Ill.—1 reprint.
Dr. Benjamin M. Berstein, F.A.C.P., Brooklyn, N. Y.—2 reprints.
Charles A. Bohnengel, F.A.C.P., Captain, (MC), AUS—1 reprint.
Dr. Barnett Greenhouse, F.A.C.P., New Haven, Conn.—1 reprint.
Dr. Herbert T. Kelly, F.A.C.P., Philadelphia, Pa.—7 reprints.
Dr. Harry R. Litchfield, F.A.C.P., Brooklyn, N. Y.—3 reprints.
Dr. Thomas H. McGavack, F.A.C.P., New York, N. Y.—3 reprints.
Dr. William Nimeh, F.A.C.P., Mexico City, D. F.—1 reprint.
Joseph F. Painton, F.A.C.P., Lieutenant Colonel, (MC), AUS—1 reprint.
Michael Peters (Associate), Captain, (MC), AUS—1 reprint.
Dr. William S. Reveno, F.A.C.P., Detroit, Mich.—1 reprint.
Morgan Y. Swirsky (Associate), Lieutenant, (MC), AUS—1 reprint.
Dr. Michael Weingarten (Associate), New York, N. Y.—1 reprint.
Dr. Alexander S. Wiener, F.A.C.P., Brooklyn, N. Y.—8 reprints.

Dr. Chester S. Keefer Appointed Governor for Massachusetts

Dr. Chester S. Keefer, F.A.C.P., Boston, was appointed, during November, by President Ernest E. Irons, the College Governor for the state of Massachusetts, to succeed the late Dr. William B. Breed. All local matters concerning the College, including proposals for membership, shall in the future be cleared through Dr. Keefer, whose address is 65 East Newton Street, Boston 18.

New Committee Appointments

Dr. George F. Strong, F.A.C.P., Vancouver, B.C., has been appointed a member of the Committee on Constitution and By-Laws, to succeed the late Dr. Charles H. Cocke. Dr. James E. Paullin, F.A.C.P., Atlanta, already a member of the Committee on Constitution and By-Laws, will serve as Chairman.

Dr. Roger I. Lee, F.A.C.P., Boston, has been appointed a member of the Committee on Educational Policy to succeed the late Dr. Charles H. Cocke.

Dr. LeRoy H. Sloan, F.A.C.P., Chicago, has been appointed a member of the Committee on Post-War Planning for Medical Service to succeed the late Dr. William B. Breed.

Resolution from Kentucky State Medical Association

The War-Time Graduate Medical Meetings Committee has coöperated during 1943 and 1944, in the program of the Kentucky State Medical Association, wherefor the following resolutions have been received:

"Whereas, The programs of the Kentucky State Medical Association for 1943 and 1944 have been most instructive and valuable as postgraduate courses for the rank and file of the profession, and

"Whereas, The success of these programs is wholly due to the splendid cooperation of the American Medical Association, the American College of Surgeons, the American College of Physicians, through the National War-Time Graduate Medical Meetings, and the essayists of national reputation whom they have furnished,

"Therefore, Be It Resolved, That the House of Delegates, being duly assembled on this 94th Annual Meeting, go on record as expressing our appreciation to these national associations for their war-time contribution to our Association and the representatives of the Armed Forces in attendance, and

"Be It Further Resolved, That this Resolution be spread upon the Minutes of this Association, and in further testimony of our appreciation, that a copy of this Resolution be forwarded to the respective associations having participated in these programs."

Opportunities for Interns and Residents in Psychiatry, St. Elizabeth's Hospital, Washington

The United States Civil Service Commission is accepting applications for War Service Appointments as medical officers (rotating interneship and psychiatric resident) for St. Elizabeth's Hospital, Washington, D. C., at $2,433.00 a year. St. Elizabeth's Hospital is an institution for the treatment of mental disorders. It has a 500-bed medical and surgical service. Full information and application forms can be obtained from the United States Civil Service Commission, Washington 25, D. C.

An Experiment by the New York Academy of Medicine—Permanent Drug Exhibit

Thirty-eight of the leading pharmaceutical companies of the United States are collaborating with the New York Academy of Medicine Committee on Drug Exhibits, of which Dr. Walter A. Bastedo, F.A.C.P., is Chairman, in an exhibit of drugs and other pharmaceuticals currently employed in combating infectious diseases.

From time to time the Committee will replace the present exhibit with a new one illustrating the latest developments in the pharmaceutical world.

The State Medical Society of Wisconsin announces its 1945 annual meeting at Milwaukee, October 7–10.

American Urological Association Offers Award

The American Urological Association offers an annual award not to exceed $500.00, for an essay (or essays) on the result of some specific clinical or laboratory research in urology. Competitors are limited to residents in urology in recognized hospitals and to urologists who have been in such specific practice for not more than five years. Essays should be submitted to the Secretary, Dr. Thomas D. Moore, 899 Madison Avenue, Memphis, Tennessee, on or before March 15, 1945.

Report from the Office of the Surgeon General, U. S. Army

Major General George F. Lull, F.A.C.P., Deputy Surgeon General of the Army, addressed the Fifth Congress of the Army Service Forces Training Agencies at Camp Barkeley,Texas, October 24–26. The purpose of the conference was to review the 1944 Army Service Forces training plan and to explain future plans.

General Lull Talks on Health of Army

Hospital admission records show there has been a striking decline in the incidence of many diseases in this war compared with the first World War, Major General George F. Lull, F.A.C.P., U. S. A., Deputy Surgeon General of the Army, told the International College of Surgeons which met at Philadelphia on October 3. The pneumonia rate, he said, has dropped from 19.0 to 12.8, the measles rate from 23.8 to 5.8, mumps from 55.8 to 6.2, scarlet fever from 2.8 to 1.6, meningococcic meningitis from 1.2 to 0.8, tuberculosis from 9.4 to 1.2 and venereal disease from 86.7 to 41.0. These figures represent annual hospital admission rates per thousand strength. Similarly the death rate from all diseases with the exception of deaths due to influenza epidemic dropped from 14.1 in World War I to 0.6. The Army's influenza rate, which was 5.97 in World War I, has become negligible, being represented statistically by 0.00 on this basis.

Recent Promotions, Medical Corps Officers

Major to Lieutenant Colonel

Samuel Morrison, F.A.C.P., Baltimore, Md.
Oliver Joseph Menard, F.A.C.P., Long Meadow, Mass.
Kendall Elsom, F.A.C.P., Philadelphia, Pa.

The Madigan General Hospital at Fort Lewis, Washington, was named in honor of the late Colonel Patrick Sarsfield Madigan, (MC), F.A.C.P., for his long and faithful service in the Army Medical Corps.

University of Maryland Honors General Kirk

Major General Norman T. Kirk, F.A.C.P., Surgeon General of the U. S. Army, recently received the honorary degree of Doctor of Science from his alma mater, the University of Maryland. The citation was read by Major General Robert U. Patterson, F.A.C.P., Dean of the Medical School and former Surgeon General of the Army. General Kirk addressed the graduates of the Schools of Medicine and Nursing and presented their diplomas. Prior to the ceremonies, Dr. Byrd, President

of the University of Maryland, and members of the faculty of the Medical School gave a dinner in honor of General Kirk at the Hotel Belvedere.

Colonel Baker Awarded Legion of Merit

Colonel Benjamin M. Baker, F.A.C.P., Baltimore, has been awarded the legion of merit by General Douglas B. MacArthur for "exceptionally meritorious conduct in the performance of outstanding services in the South Pacific Area from April 20, 1942, to June 13, 1944."

The National Committee for Mental Hygiene has elected Major General Norman T. Kirk, F.A.C.P., The Surgeon General, as one of its six new members in recognition of his "unusual awareness of the importance of skilled psychiatric treatment in the Army."

Dr. Carl V. Moore, F.A.C.P., Associate Professor of Medicine, Washington University, St. Louis, Mo., is a recent appointee to the Army Epidemiological Board.

Army Medical Consultants Convene at White Sulphur Springs

The Service Command Consultants in Medicine and civilian physicians who are Consultants in Medicine to The Surgeon General and the Secretary of War convened at White Sulphur Springs, Va., October 30–31. Among those in attendance were Major General Norman T. Kirk, F.A.C.P., The Surgeon General, Colonel W. Paul Holbrook, F.A.C.P., Chief of Professional Service, Army Air Forces, Colonel Arden Freer, F.A.C.P., Chief of Professional Administrative Service, Lieutenant Colonel Francis R. Dieuaide, F.A.C.P., Chief of Tropical Disease Treatment Branch, Brigadier General Hugh J. Morgan, F.A.C.P., Chief Consultant in Medicine to The Surgeon General, Colonel Walter Bauer, F.A.C.P., Consultant in Medicine, Eighth Service Command, Colonel E. V. Allen, Consultant in Medicine, Seventh Service Command and Lieutenant Colonel Joseph A. Hayman, Jr., F.A.C.P., Chief of Medical Service, Moore General Hospital, Swannanoa, N. C.

Lieutenant Colonel Phillip T. Knies, F.A.C.P., of Columbus, Ohio, Army member of the Interdepartmental Quarantine Commission, has been assigned as Army Quarantine Liaison Officer to The Surgeon General of the Army and is stationed in the Epidemiology Division, Preventive Medicine Service.

Wakeman Field Sanitary Area Dedicated

A model sanitary demonstration area was dedicated in October at Carlisle Barracks, Pa. It has been named Wakeman Field in memory of the late Colonel Frank B. Wakeman, F.A.C.P., who was Director of the Training Division, Office of The Surgeon General and former Instructor in the Department of Military Sanitation at Carlisle Barracks. Guest speakers stressed the importance of rigid sanitary measures in the field to prevent the spread of disease.

Army Trains Clinical Psychologists

An officers course in clinical psychology was inaugurated in October at the Adjutant General's School, Fort Sam Houston, Tex. The welcoming address was given by Lieutenant Colonel James B. Polka, Chief of the neuropsychiatry section of Brooke General Hospital, Fort Sam Houston, Tex., who represented Brigadier General George C. Beach, Jr., F.A.C.P., the hospital's Commanding General. Lieutenant Colonel Morton G. Seidenfeld, AGD, Chief Clinical Psychologist and Liaison with the Office of The Surgeon General, spoke on the duties and responsibilities of the clinical psychologist.

Representing The Surgeon General, Lieutenant Colonel Malcolm J. Farrell, MC, Assistant Director of the Neuropsychiatry Consultants Division, spoke on the relationship between the psychologist and psychiatrist in Army hospitals.

The new course will train officers who are clinical psychologists to deal with neuropsychiatric patients in Army hospitals. It includes a review of testing and interview technics, Army hospital procedures, types of problems encountered, diagnosis, clinical technics and therapeutic measures. A clinical psychologist is being detailed to the neuropsychiatric section of every Army hospital having a thousand or more beds.

Gorgas Medal Presented to James J. Sapero

Commander James J. Sapero (Associate), (MC), USN, is this year's recipient of the Gorgas Medal, for distinguished service as an Officer of the Medical Corps, U. S. Navy, in the field of malaria and preventive medicine. It was presented at the annual dinner of the Association of Military Surgeons, at New York, November 3, 1944. The award is sponsored by Wyeth Incorporated, and was established in memory of Surgeon General William Crawford Gorgas, whose work in preventive medicine made possible construction of the Panama Canal.

The Michigan State Medical Society announces its 1945 annual session to be held in Detroit, September 19–21.

Major George C. McEachern (Associate) has recently been made Chief of the Medical Service at the Army Air Force Regional and Debarkation Hospital, Hamilton Field, Calif. Major McEachern was previously Chief of the Rheumatic Fever Service at Buckley Field, Colo. He published his experiences in "The Treatment of Acute Rheumatic Fever with Penicillin," in the *Journal of the A. M. A.*, September 30, 1944.

Colonel Maurice C. Pincoffs, F.A.C.P., is now Chief of Professional Services, Southwest Pacific Area, U. S. Army.

Dr. O. H. Perry Pepper, F.A.C.P., Philadelphia, has been appointed on a Board of Honorary Consultants of the Army Medical Library by The Surgeon General.

Lieutenant Colonel Joseph Vander Veer (Associate), Philadelphia, is now Commanding Officer of the 364th Station Hospital, A. P. O. No. 322, Unit 1, San Francisco, Calif.

The Montreal Medico-Chirurgical Society conducted its 12th annual clinical convention in Montreal, October 16–21. This convention was conducted as a post-graduate course and was open to all practitioners not only in the Province of Quebec, but in the neighboring Provinces, as well as the adjoining States. There are four

other smaller clinical meetings held during the year for the same postgraduate teaching. Numerous Montreal institutions coöperate.

Commander Christopher C. Shaw, F.A.C.P., (MC), USNR, was commissioned a Lieutenant Commander in the Medical Corps of the U. S. Naval Reserve on July 28, 1940, from Bellows Falls, Vt., where he was engaged in the practice of internal medicine. He was ordered to active duty on May 19, 1941, and was first assigned to the U. S. Naval Hospital at Chelsea, Mass. One month later he was transferred to the U. S. Naval Station, Portsmouth, N. H., as Physician to the Naval Prison. From August 1 to September 30, 1941, he was a student at the School of Aviation Medicine, U. S. Naval Air Station, Pensacola, Fla., and remained there as a member of the faculty, Instructor in Cardiology. In early 1943, he was promoted to the rank of Commander and was designated a Flight Surgeon by the Bureau of Aeronautics, Navy Department. He became Senior Medical Officer at the U. S. Naval Auxiliary Air Station, Whiting Field, Fla., and later in the year was ordered to duty as Senior Medical Officer and Flight Surgeon of the Aircraft carrier, U. S. S. Solomons. He participated in the invasion on D-Day, and is at sea in the combat zones, Atlantic and/or Pacific. Since his entry on active duty, he has found time and the opportunity to publish articles on "Aviation Medicine" and "Heart Disease of Middle Age."

Photos from Dr. White's Postgraduate Course

During the American College of Physicians Postgraduate Course in Cardiology, at Boston, October 2–7, under Dr. Paul White, F.A.C.P., many photographs were taken of the group at Massachusetts General Hospital and of various members of the faculty "in action," by Dr. Leslie French, F.A.C.P., Suite 215, 1726 Eye St., N. W., Washington, D. C. Dr. French announces that the prints are now available to any member of the course who may want them as mementos.

Regional Meetings

The popularity and practicability of the regional meeting program of the College has been further demonstrated by the increasing interest and attendance at those recently conducted, as well as by the interest being shown in future scheduled meetings. Statistics of attendance are shown below for three of the recent meetings. It should be remembered, however, that different territories vary greatly in the number of College members and the number of medical officers in the Armed Forces. The regional meetings, therefore, are not comparable.

New York Regional Meeting, October 20, 1944—Officially 266 registered at the morning and afternoon programs; an evening attendance at the panel discussion on "Evaluation of Sulfa Drugs and Penicillin" of approximately 460, of whom more than two-thirds were Fellows and Associates of the College.

Omaha, October, 23–27, 1944—A combined War-Time Graduate Medical Meeting, certified as part of the Omaha Mid-West Clinical Society session. The total attendance at the meeting was 924, including 51 military officers from the surrounding posts. Twenty-one members of the American College of Physicians made presentations, as did also the Executive Secretary, Mr. E. R. Loveland, and the Associate Director of the American College of Surgeons, Dr. Malcolm T. MacEachern.

Chicago Regional Meeting, November 4, 1944—Embracing Illinois, Indiana, Iowa, Kentucky, Michigan, Minnesota and Wisconsin.

	Fellows	Associates	Guests	Total
Army	18	14	39	71
Navy	3			3
U. S. Public Health Service		1	3	4
Total, Servicemen	21	15	42	78
Civilians	182	37	75	294
	203	52	117	372

Thirty-four States, the District of Columbia and Canada were represented. The primary reason for the national distribution of attendants was due to the fact that this Regional Meeting concluded the two-weeks' postgraduate course in Special Phases of Internal Medicine, under the auspices of the College in Chicago. There were officially registered in the course 157 physicians, with a number of additional visitors.

Pittsburgh Regional Meeting, November 11, 1944—Embracing Western Pennsylvania, Ohio and West Virginia.

	Fellows	Associates	Guests	Total
Army	4	1	5	10
Navy				
U. S. Public Health Service	—	—	—	—
Total, Servicemen	4	1	5	10
Civilians	78	23	56	157
	82	24	61	167

The attendance was largely centered among members of the College from Western Pennsylvania, Ohio and West Virginia, but there was a scattered few from neighboring territory.

Philadelphia, December 15, 1944—Embracing Eastern Pennsylvania, New Jersey, and Delaware, in conjunction with the postgraduate course in Special Medicine at Philadelphia Institutions, December 4–15, and the annual meetings of the Committees and Regents of the College, December 15–16.

PROGRAM

THOMAS M. MCMILLAN, M.D., F.A.C.P.

General Chairman and Acting Governor for Eastern Pennsylvania

Friday, December 15, 1944

MORNING SESSION—9:30 a.m.—12:00 m.

Jefferson Medical College Hospital

1020 Sansom Street

(Clinical Amphitheatre, First Floor)

Presiding Officer

WILLIAM HARVEY PERKINS, M.D., F.A.C.P.

1. Short Notes on the Rh Factor.
   LOWELL ASHTON ERF, M.D., F.A.C.P., Associate in Medicine, Jefferson Medical College of Philadelphia.

2. Neurological Complications of Spinal Anaesthesia.
   HYMAN E. YASKIN, M.D. (by invitation), Demonstrator of Neurology, Jefferson Medical College of Philadelphia.
3. The Origin and Clinical Significance of Muscle Fasciculations.
   FRANCIS M. FORSTER, M.D. (by invitation), Assistant Professor of Neurology, Jefferson Medical College of Philadelphia, and
   BERNARD J. ALPERS, M.D. (by invitation), Professor of Neurology, Jefferson Medical College of Philadelphia.
4. Prolonged Fever.
   HOBART A. REIMANN, M.D. (by invitation), Professor of Medicine and Acting Head of Department of Experimental Medicine, Jefferson Medical College of Philadelphia.
5. Present Status of the Leukemia Problem.
   FRANKLIN R. MILLER, M.D. (by invitation), Associate Professor of Medicine, Jefferson Medical College of Philadelphia.
6. Some Psychological Factors in Obesity.
   ROBERT A. MATTHEWS, M.D. (Associate), Associate Professor of Psychiatry and Head of Department in absence of Colonel Baldwin L. Keyes, F.A.C.P., Jefferson Medical College of Philadelphia.
7. The Treatment of Rheumatic Chorea with Fever Therapy.
   EDWARD L. BAUER, M.D. (by invitation), Professor of Pediatrics, Jefferson Medical College of Philadelphia.

LUNCHEON

(Buffet)

12:30 p.m.

COLLEGE HEADQUARTERS

4200 Pine Street, Philadelphia, Pa.

AFTERNOON SESSION—2:45 p.m.

Ballroom

Benjamin Franklin Hotel

9th and Chestnut Streets

Presiding Officer

THOMAS M. McMILLAN, M.D., F.A.C.P.

SYMPOSIUM ON RHEUMATIC FEVER

1. Some of the Clinical Problems of Rheumatic Fever.
   T. DUCKETT JONES, M.D. (by invitation), Assistant Professor of Medicine, Harvard Medical School; Director of Research, House of the Good Samaritan; Assistant Visiting Physician, Massachusetts General Hospital; Boston, Mass.
2. The Epidemiology of Rheumatic Fever.
   JOHN R. PAUL, M.D. (by invitation), Professor of Preventive Medicine, Yale University School of Medicine, New Haven, Conn.
3. The Council on Rheumatic Fever: Its Origin, Purposes and Present Status.
   H. M. MARVIN, M.D. (by invitation), Associate Clinical Professor of Medicine, Yale University School of Medicine; Acting Executive Secretary, American Heart Association, New Haven, Conn.

4. The Problem of Rheumatic Fever in the Armed Forces.
W. PAUL HOLBROOK, M.D., F.A.C.P., Colonel, (MC), AUS, Chief of the Professional Division, Office of the Air Surgeon, Washington, D. C.

EVENING PROGRAM

Benjamin Franklin Hotel

9th and Chestnut Streets

6:30 p.m.—Reception and Cocktail Party

Betsy Ross Room, Mezzanine Floor

7:30 p.m.—Dinner (Informal)

Ballroom, Benjamin Franklin Hotel

Toastmaster: HENRY L. BOCKUS

Introduction of Distinguished Guests

(A few brief talks; no formal addresses)

Memphis, January 25–26, 1945—Embracing Tennessee, Arkansas, Louisiana and Eastern Texas; Dr. William C. Chaney, Chairman, Governor for Tennessee. The program for this meeting is not yet available but is in process of preparation with the assistance of the American College of Physicians Governors for the participating states, namely, Dr. Edgar Hull, New Orleans, Governor for Louisiana, Dr. John G. Archer, Greenville, Governor for Mississippi; Dr. Oliver C. Melson, Little Rock, Governor for Arkansas; Dr. M. D. Levy, Houston, Governor for Texas. This meeting is expected to develop as one of the largest, most popular and really valuable regional meetings the College has conducted. It will be highlighted by the presence of several distinguished medical officers from the Army and Navy, including the Surgeons General or their official envoys. The program will be ready for distribution in late December, and will be mailed to all members and medical installations of the Army, Navy and Public Health Service in the territory mentioned. Physicians outside of the territory may obtain programs on request to the Executive Offices of the College. Cordial invitation is extended to every interested physician or medical officer, whether he be a member of the College or not.

Oklahoma City, February 23, 1945—Embracing Oklahoma, Kansas, Northwestern Texas, Missouri and Nebraska; Dr. Lea A. Riely, Chairman, Governor for Oklahoma. This will be the first regional meeting of its character in the Oklahoma City district. Chairman Riely is receiving the assistance and coöperation of the College Governors of the territory, including Dr. Harold Jones, Winfield, Governor for Kansas; Dr. M. D. Levy, Houston, Governor for Texas; Dr. Ralph Kinsella, St. Louis, Governor for Missouri; Dr. Warren Thompson, Omaha, Governor for Nebraska. While Nebraska has already held a regional meeting under date of October 26, in conjunction with the Omaha Mid-West Clinical Society, the State will also coöperate with the meeting in Oklahoma City. The Oklahoma City Internists Club will hold a meeting on February 22, to which members of the College will be invited. The Regional Meeting of the College follows on February 23, and members of the Oklahoma City Internists Club are invited, as are also medical officers of the Army, Navy and Public Health Service. This meeting has been planned for a considerable period of time and great care is being exercised in selection of subjects of especially timely interest given by recognized authorities in each field. The Chairman, Dr. Riely, has been a Governor of the American College of Physicians for about twenty years; his labors have always been characterized by the deepest interest in the welfare of the College and the medical profession; he is the dean of internists in his territory, and it is predicted that the Oklahoma members will rally to his assistance in organizing a memorable meeting in his honor.

The following letters from the Surgeons General Kirk and McIntire, which were published in the Bulletin of the War-Time Graduate Medical Meetings, indicate their interest in and approval of these meetings.

"The Army is very grateful to the Central Committee for the War-Time Graduate Medical Meetings it has been carrying on throughout the various parts of the United States in our Army hospitals. Both General Rankin and General Morgan, Consultants in Surgery and Medicine, Surgeon General's Office, feel that these meetings have been of great service as a morale builder, as well as informative to our medical officers serving at these various installations. It is their desire and mine that this work be continued for at least another year.

"Like you, I realize that the doctors in our hospitals have much more to do and this will increase as more battle casualties arrive from overseas and the number of medical officers available here at home to do the job declines. I feel that your Regional Chairmen through their contact with the commanding officers of these installations will be able to determine the advisability of scheduling meetings, their scope and the availability of doctor-hours in these hospitals to attend them.

"Many thanks again to you and your Committee and to the Regional Chairmen for the grand job that you have been doing for us."

NORMAN T. KIRK,
Major General, U. S. Army,
The Surgeon General.

"I have visited a great number of our institutions throughout the country during the past year and have had the opportunity of talking with numerous officers regarding the value of the War-Time Graduate Medical Meetings. The consensus is that they are of great help. I know from personal experience that they also have added value in bringing together the members of the medical profession in civil life and in the Services. In addition to this you are bringing to our institutions invaluable experience from qualified teachers throughout the nation and it can not but have a helpful affect in the war effort.

"I hope you will find it possible to continue these meetings throughout the coming year. As in the past, the Navy will co-operate in every way possible to make them a success."

ROSS T. MCINTIRE,
Vice Admiral, U. S. Navy,
The Surgeon General.

A. C. P. POSTGRADUATE COURSES

The continued popularity of the postgraduate courses offered by the American College of Physicians is again manifested by practically all courses being oversubscribed during the autumn of 1944. Readers may be interested in the following statistics of attendance.

Summary of Registration, A. C. P. Postgraduate Courses, Autumn, 1944

	Civilian Physicians	Service Medical Officers	Total	Grand Totals
Course No. 1, Cardiology, Boston, Oct. 2–7.				
Members, A. C. P.:				
Fellows	42	2	44	
Associates	11	3	14	
			58	
Non-Members	8	5	13	71

Course No. 2, General Medicine, Portland, Oct. 9–14.				
Members, A. C. P.:				
Fellows	11	1	12	
Associates	1	2	3	
			15	
Non-Members	2	1	3	18
Course No. 3, Internal Medicine, Minneapolis, Oct. 9–14.				
Members, A. C. P.:				
Fellows	10	1	11	
Associates	8	3	11	
			22	
Non-Members	10	11	21	43
Course No. 4, Allergy, New York City, Oct. 9–14.				
Members, A. C. P.:				
Fellows	16	3	19	
Associates	5	2	7	
			26	
Non-Members	23	10	33	59
Course No. 5, Internal Medicine, Chicago, Oct. 23–Nov. 4.				
Members, A. C. P.:				
Fellows	47	12	59	
Associates	18	10	28	
			87	
Non-Members	38	54	92	179
* *Course No. 6, Special Medicine, Philadelphia, Dec. 4–15.*				
Members, A. C. P.:				
Fellows	25	7	32	
Associates	7	5	12	
			44	
Non-Members	8	25	33	77*
	290	157		447

* Advanced Registration, Not Final.

Tentative Roster, Spring, 1945

Full announcement of the roster will appear in the next issue of this journal. At the present time, it is planned to give five courses: Cardiovascular Diseases; Gastrointestinal Diseases; Internal Medicine; Clinical Medicine, with Special Emphasis upon the Hematological Viewpoint; Applications of Psychiatry to the Practice of Internal Medicine.

Fees and other regulations will be the same as heretofore. Medical officers of the Armed Forces will be admitted free; members of the College will pay a tuition fee of $20.00 per week; non-members, $40.00 per week.

The Massachusetts General Hospital, Boston, through its general Executive Committee, has established a Staff Memorial Fund to which contributions may be made in honor of the memory of any staff member. The plan grew out of a wish to honor Dr. William B. Breed, F.A.C.P., who died August 21. Dr. Breed had been a member of the general Executive Committee and had served the Massachusetts General Hospital for 25 years.

The faculty and alumni of Western Reserve University School of Medicine on September 25, honored their former Dean and former Professor of Pharmacology, Dr. Torald H. Sollmann, F.A.C.P., at a dinner. They presented him with a silver plaque in recognition of his distinguished services. Dr. Sollmann was associated with Western Reserve University for nearly 50 years. He is now Chairman of the Council on Pharmacy and Chemistry of the American Medical Association.

Dr. Samuel E. Thompson, F.A.C.P., Kerrville, has resigned as a member of the Texas State Board of Health.

Dr. John Walker Moore, F.A.C.P., Dean of University of Louisville School of Medicine, was made president-elect of the Association of American Medical Colleges at its annual meeting in Detroit, October 23–25. Dr. William S. McEllroy, F.A.C.P., Dean of the University of Pittsburgh School of Medicine was elected vice-president. Dr. Walter A. Bloedorn, F.A.C.P., Dean of George Washington University School of Medicine, Washington, D. C., and Dr. Wilburt C. Davison, F.A.C.P., Dean of Duke University School of Medicine, Durham, N. C., were elected members of the Executive Council of the Association, succeeding Dr. Willard C. Rappleye, F.A.C.P., Dean of Columbia University College of Physicians and Surgeons, and Dr. Russell H. Oppenheimer, F.A.C.P., Dean of Emory University School of Medicine, Atlanta.

Colonel Otis O. Benson, Jr., Honored

Colonel Otis O. Benson, Jr. (Associate), (MC), U. S. Army, has been awarded the legion of merit by the War Department, his citation reading, "In his capacity as Chief of Aero Medical Research at Wright Field from September 6, 1940, to July 15, 1943, he was responsible for successfully developing, testing and standardizing all items of medical equipment used in connection with military aviation. His professional skill and organizing ability made it possible for his unit, during a period of rapidly changing requirements, to succeed in applying previously known principles of aviation medicine to the practical situations of modern warfare and solving new problems arising from unexpected developments in aerial combat."

Dr. Louis H. Bauer, F.A.C.P., Hempstead, N. Y., addressed the Fairfield County Medical Association in Stamford, Conn., October 4, on "The Future of Prepayment Medical Plans."

On November 2, Dr. Edward A. Strecker, F.A.C.P., Philadelphia, delivered the 17th annual Pasteur Lecture of the Institute of Medicine of Chicago. Dr. Strecker's subject was "War Psychiatry and Its Influence on Post-War Psychiatry and Civilization."

The late Dr. Andrew P. Biddle, F.A.C.P., Detroit, who died on August 2, 1944, bequeathed approximately $40,000.00 to the Michigan State Medical Society, of which he had formerly been president, for use in the furtherance of its program of postgraduate medical education.

Dr. Oswald T. Avery, Phillips Medalist of the American College of Physicians in 1932, was awarded the Gold Medal of the New York Academy of Medicine "for distinguished service in medicine" at a meeting on October 5. The presentation was made by Dr. Arthur F. Chace, F.A.C.P., President of the Academy.

Dr. Edward B. Krumbhaar, F.A.C.P., Professor of Pathology, University of Pennsylvania School of Medicine and Graduate School of Medicine, has been elected an honorary Fellow of the Royal Society of Medicine, London.

Dr. Kenneth E. Appel, F.A.C.P., Philadelphia, was recently elected president-elect of the Pennsylvania Psychiatric Society.

The Southern Medical Association conducted its 38th annual meeting at St. Louis, Mo., November 13–16. Among those on the program were: Col. Howard A. Rusk, F.A.C.P., "New Horizons in Medicine"; Capt. Alphonse McMahon, F.A.C.P., "Civilian Tropical Disease Problems Following Demobilization"; Dr. Charles F. Mohr, F.A.C.P., Baltimore, "Results of Penicillin Treatment in Neurosyphilis"; Dr. Harry S. Bernton, F.A.C.P., Washington, D. C., "Castor Bean Sensitiveness"; Dr. Cornelius O. Bailey, F.A.C.P., Los Angeles, "Post-war Medical Education."

The Medical Society of Virginia held its annual meeting in Richmond recently, with an attendance of 570 doctors. Dr. H. B. Mulholland, F.A.C.P., of Charlottesville, succeeded to the presidency. Dr. Philip S. Smith, F.A.C.P., of Abingdon, is a vice-president, and Dr. C. Lydon Harrell, F.A.C.P., of Norfolk, is a Councilor from the Second District. The Society will hold its 1945 session in Roanoke.

Dr. Robert H. Bayley, F.A.C.P., has been appointed Professor of Clinical Medicine and Vice Chairman of the Department of Medicine of the University of Oklahoma School of Medicine. Dr. Bayley for several years was Associate Professor of Medicine at the Louisiana State University School of Medicine, New Orleans.

The Oklahoma City Clinical Society conducted its 14th annual fall clinical conference in Oklahoma City, October 23–26. Among the guest lecturers were the following: Dr. Tinsely R. Harrison, F.A.C.P., Dallas, Tex., "Abdominal Disorders Simulating Coronary Artery Disease" and "Recent Concepts of Hypertension";

Dr. Ralph A. Kinsella, F.A.C.P., St. Louis, Mo., "Arthritis" and "Etiology, Diagnosis, and Treatment of Acute Dilatation of the Heart"; Dr. Bruce K. Wiseman, F.A.C.P., Columbus, Ohio, "Primary Atypical or Virus Pneumonia" and "The Leukemias."

A large proportion of the Fellows of the College in the Oklahoma City district contributed also to the program.

The Dallas Southern Clinical Society will hold its 15th annual spring clinical conference at Hotel Adolphus, Dallas, March 19–22, 1945. Among the guest speakers will be Dr. J. Arnold Bargen, F.A.C.P., Rochester, Gastro-enterology; Dr. Charles A. Doan, F.A.C.P., Columbus, Ohio, Internal Medicine; Dr. William Henry Sebrell, Jr., F.A.C.P., U. S. Public Health Service, Washington, D. C., Basic Science; and Dr. George W. Thorn, F.A.C.P., Boston, Mass., Internal Medicine.

Dr. Irvine H. Page, F.A.C.P., for the past seven years Director of the Eli Lilly Laboratory for Clinical Research, Indianapolis, will become Director of Research at the Cleveland Clinic, Cleveland, on January 1.

Dr. Oscar O. Miller, F.A.C.P., Louisville, was inducted into the presidency of the Kentucky State Medical Association at its last annual meeting in Lexington.

Dr. Carl V. Moore, F.A.C.P., Associate Professor of Medicine, Washington University School of Medicine, St. Louis, was among the first of a group of visiting professors to the University of Louisville School of Medicine under a grant for this purpose by the Commonwealth Fund.

Dr. John H. Musser, F.A.C.P., and Dr. Julius L. Wilson, F.A.C.P., both of New Orleans, are president and medical consultant, respectively, of the newly chartered and organized Tuberculosis Association of New Orleans.

Dr. Thomas Parran, F.A.C.P., Surgeon General of the U. S. Public Health Service, gave the commencement address before the University of Utah School of Medicine, Salt Lake City, on September 10. Dr. Parran received the honorary degree of Doctor of Science. This is the first graduation exercises of this new four-year medical school.

Brigadier General Eugen Reinartz, F.A.C.P., (MC), U. S. A., was installed as President of the Aero Medical Association of the United States at its meeting in St. Louis on September 4.

Dr. George H. Anderson, F.A.C.P., Spokane, has been elected president-elect of the Washington State Medical Association for the coming year.

Dr. Lewis G. Allen, F.A.C.P., Kansas City, Kan., has succeeded to the presidency of the Radiological Society of North America.

Dr. Lyell C. Kinney, F.A.C.P., San Diego, has succeeded to the presidency of the American Roentgen Ray Society.

Dr. George M. Lewis, F.A.C.P., New York, addressed the New York State Association of Public Health Laboratories at Albany, November 17, on "Clinical and Immunological Aspects of Fungus Infection."

Dr. Frank R. Menne, F.A.C.P., has resigned as Professor and Head of the Department of Radiology at the University of Oregon Medical School, Portland, with which institution he has been associated for 28 years.

Dr. J. Winthrop Peabody, F.A.C.P., Washington, D. C., has been made an honorary member of the Sociedad Chilena de Tisiologia.

Under the presidency of Dr. Felix J. Underwood, F.A.C.P., Jackson, Miss., the American Public Health Association conducted its second war-time public health conference and its 73rd annual business meeting in New York, October 2–5.

The September issue of the *Mississippi Doctor* was dedicated to Dr. Underwood, who is the Mississippi State Health Officer.

Colonel Neely C. Mashburn, F.A.C.P., has become Surgeon of the A. A. F. Training Command, Fort Worth, Tex., succeeding Brigadier General Charles R. Glenn, who has been appointed Deputy Air Surgeon of the Army Air Forces, headquarters in Washington, D. C.

War-Time Graduate Medical Meetings

Region No. 1 (Maine, New Hampshire, Vermont, Massachusetts) and Region No. 2 (Connecticut, Rhode Island)—New England Committee for War-Time Graduate Medical Meetings—Dr. W. R. Ohler, Chairman; Dr. L. E. Parkins, Secretary; Dr. S. B. Weld, Dr. A. M. Burgess, Dr. C. S. Keefer, Dr. F. T. Hill, Dr. J. P. Bowler, Dr. B. F. Cook, Executive Committee members

Station Hospital, Dow Field, Bangor, Maine

December 21 Head, Spine and Nerve Injuries

Dispensary, U. S. Naval Air Station, Brunswick, Maine

December 21 Burns and Reconstruction Surgery

Station Hospital, Fort Williams, Portland, Maine

December 21 The Skin

Station Hospital, Presque Isle, Maine

December 21 Stomach, Biliary Tract, Intestinal Disorders

Dispensary, U. S. Naval Construction Training Center, Quoddy Village

December 21 Pilonidal Sinus and Common Diseases of the Anus and Rectum

Station Hospital, Grenier Field, Manchester, New Hampshire

December 20 Peripheral Vascular Disease

U. S. Naval Hospital, Portsmouth, New Hampshire

December 21 Diarrheal Diseases

Boston Area Station Hospital, Waltham, Massachusetts

December 21 The Use of Penicillin and the Sulfa Drugs

U. S. Naval Hospital, Chelsea, Massachusetts

December 21 Blood Dyscrasias and Transfusions

Lovell General Hospital, Fort Devens, Massachusetts

December 21 The Pneumonias and Other Respiratory Infections

Station Hospital, Camp Edwards, Massachusetts

December 21 The Psychoneuroses and Their Management

Cushing General Hospital, Framingham, Massachusetts

December 21 Contagious Diseases and Complications

Station Hospital, Camp Myles Standish, Taunton, Massachusetts

December 21 Cardiac Neuroses, Cardiac Emergencies, Cardiac Rehabilitation

U. S. Marine Hospital, Brighton, Massachusetts

December 21 Acute Infections of the Central Nervous System

Station Hospital, Westover Field, Chicopee Falls, Massachusetts or U. S. Naval Convalescent Hospital, Springfield, Massachusetts

December 21 Tropical Diseases, to Include Malaria and Other Insect-Borne Diseases

Dispensary, U. S. Naval Construction Training Center, Davisville, Rhode Island

December 21 Joint Injuries

U. S. Naval Hospital, Newport, Rhode Island

December 21 Fractures of Extremities

Station Hospital, Bradley Field, Windsor Locks, Connecticut

December 21 Fractures of Extremities

Air Corps Station Hospital, New Haven, Connecticut

December 21 Chest and Abdominal Injuries

Station Hospital, Fort H. G. Wright, Fishers Island, New York

December 21 Acute Abdominal Emergencies

REGION No. 4 (Eastern Pennsylvania, Delaware, New Jersey)—Dr. B. P. Widmann, Chairman; Dr. J. S. Rodman, Dr. S. P. Reimann.

U. S. Naval Hospital, Philadelphia, Pennsylvania

January 26 Common Mistakes in the Diagnosis of Treatment of Gastrointestinal Diseases—Dr. Henry L. Bockus

REGION No. 8 (Western Pennsylvania, Ohio)—Dr. C. A. Doan, Chairman; Dr. P. G. Smith, Dr. F. M. Douglass.

Crile General Hospital, Cleveland, Ohio

January 23 Polycythemia—Dr. Russell H. Haden

REGION No. 14 (Indiana, Illinois, Wisconsin)—Dr. W. O. Thompson, Chairman; Dr. N. C. Gilbert, Dr. W. H. Cole, Dr. W. D. Gatch, Dr. R. M. Moore, Dr. H. M. Baker, Dr. E. R. Schmidt, Dr. E. L. Sevringhaus, Dr. F. D. Murphy.

Camp McCoy, Wisconsin

January 3 Peptic Ulcer and Gastritis—Dr. Carl W. Eberbach
January 17 Chemotherapy (Present Status)—Dr. Harry Beckman
January 31 Gall Bladder and Liver Disease—Dr. Erwin R. Schmidt

Truax Field, Wisconsin

January 3 Chronic Chest Diseases and Disease of the Larynx—Dr. John D. Steele
January 17 Head and Spine Injuries—Dr. T. C. Erickson
January 31 Allergic States—Dr. Theodore L. Squier

Mayo General Hospital, Galesburg, Illinois

January 3 Plexus and Peripheral Nerve Injuries
January 17 Dermatological Diseases
January 31 Burns and Plastic Surgery

Vaughan General Hospital, Illinois

January 3 Burns and Plastic Surgery
January 17 Malignancies in the Army Age Group—Medical X-Ray and Surgical Diagnosis and Treatment
January 31 Endocrinology

Camp Ellis, Illinois

January 3 Endocrinology
January 17 Virus and Rickettsial Diseases—Medical and Neurological Diseases and Treatment
January 31 Psychosomatic Medicine

Chanute Field, Illinois

January 3 Heart Disease and Allied Conditions
January 17 Repair of Bone in Fractures and Diseases
January 31 Arterial Vascular Disease—Traumatic Lesions

REGION No. 16 (Missouri, Kansas, Arkansas, Oklahoma)—Dr. F. D. Dickson, Chairman; Dr. O. P. J. Falk, Dr. H. H. Turner.

Station Hospital, Rosecrans Field, St. Joseph, Missouri

January 11 Chemotherapy
Trauma of the Abdomen

Regional Hospital, Fort Riley, Kansas

January 11 Allergy
Nutritional Deficiency Diseases
January 25 Clinical Psychiatry
Neurology

Station Hospital, Army Air Field, Great Bend, Kansas

January 4 - Shock, Burns and Blood Derivatives
Clinical Psychiatry
January 18 Venereal Diseases and Urology
Anesthesia

Winter General Hospital, Topeka, Kansas

January 18 Gastrointestinal Diseases—Dr. Carl R. Ferris
General Surgery—Dr. Claude J. Hunt

Postgraduate Course in Medicine by Woman's Medical College of Pennsylvania

Dr. William G. Leaman, Jr., F.A.C.P., Professor of Medicine at the Woman's Medical College of Pennsylvania, has announced the following lecture schedule for the Postgraduate Course in Medicine at the Woman's Medical College of Pennsylvania for the latter part of 1944 and the early part of 1945. The average attendance has been 45. This course has been conducted each winter.

November 22, 1944—7:00 to 9:00 p.m. Coronary Disease; Digitalis Therapy. William D. Stroud, F.A.C.P., Professor of Cardiology, University of Pennsylvania Graduate School of Medicine.

December 6, 1944—7:00 to 9:00 p.m. Recent Trends in the Treatment of Cardiovascular Disease. William G. Leaman, Jr., F.A.C.P., Professor of Medicine, and Samuel Bellet (Associate), Associate Clinical Professor of Medicine, Woman's Medical College of Pennsylvania.

January 3, 1945—7:00 to 9:00 p.m. Recent Advances in Hematology. Leandro M. Tocantins (Associate), Associate Professor of Medicine, Jefferson Medical College.

January 17, 1945—7:00 to 9:00 p.m. Recent Advances in Our Knowledge of Kidney Disease. Edward Weiss, F.A.C.P., Professor of Clinical Medicine, Temple University School of Medicine.

January 31, 1945—7:00 to 9:00 p.m. Practical Aspects of Essential Hypertension. Edward Weiss, F.A.C.P.

February 14 and 28 will be devoted to Gastrointestinal Tract; March 14 to Endocrinology; March 28, April 11 and 25, to Parasitology and Tropical Medicine. The speakers for these occasions will be announced early in January.

Brigadier General Simmons Receives Walter Reed Medal

On November 15, 1944, at the annual meeting of the American Society of Tropical Medicine, in St. Louis, Mo., the Society presented to Brigadier General James Stevens Simmons, F.A.C.P., U. S. A., Chief, Preventive Medicine Service, Office of The Surgeon General, U. S. Army, the Walter Reed Medal in recognition of meritorious achievement in tropical medicine, and for outstanding work in safeguarding the health of American troops.

The Walter Reed Medal was established by the Society in 1934 to be awarded periodically in recognition of meritorious achievement in tropical medicine by an individual or an institution.

The medal has been awarded on four previous occasions. In 1936, one medal was awarded posthumously to Major Walter Reed for his experimental work on yellow fever and another to the Rockefeller Foundation for its study and control of yellow fever. In 1939 the award was made to Dr. William B. Castle, F.A.C.P., of Harvard University and in 1940 to Dr. Herbert Clark of the Gorgas Memorial Laboratory in Panama. In 1942 two medals were awarded, one posthumously to Dr. Carlos J. Finlay for his work on yellow fever and the other to The United States of Brazil "for outstanding work in the eradication of *Anopheles gambiae* in Brazil."

At the recent meeting, General Simmons was also chosen as "President Elect" of the American Society of Tropical Medicine.

SPECIAL NOTICES

A course in Electrocardiographic Interpretation for *graduate physicians* will be given at Michael Reese Hospital by Dr. Louis N. Katz, Director of Cardiovascular Research. The class will meet each week, starting Wednesday, February 14 for 12 weeks, from 7:00 to 9:00 p.m.

Further information and a copy of the program may be obtained on application to the Cardiovascular Department, Michael Reese Hospital.

The Executive Board of the American Public Health Association announces that the Third Wartime Conference and 74th Annual Meeting, and meetings of related organizations, will be held in Chicago, Illinois, the week of September 17, 1945, with headquarters in the Hotel Stevens.

At its Annual Meetings, this professional society of public health workers brings together the health officials of the Western Hemisphere for discussion of local, national and international health problems. The Chicago program will cover subjects of interest to health officers, public health nurses, laboratory workers, nutritionists, vital statisticians, engineers, child and maternal health specialists, health educators, public health dentists, epidemiologists, industrial hygienists and others working in the broad field of health protection and promotion.

The related organizations will include the American School Health Association, the Conference of State and Municipal Public Health Engineers, of Public Health Nursing Directors, of Professors of Preventive Medicine, of State and Provincial Public Health Laboratory Directors, of State Directors of Public Health Education, and of Industrial Health Consultants.

The Illinois Committee in charge of local arrangements will be headed by Dr. Herman N. Bundesen, President, Chicago Board of Health, and Dr. Roland R. Cross, State Director of Public Health, Springfield, Illinois, Co-Chairmen.

The headquarters office of the American Public Health Association is located at 1790 Broadway, New York 19, N. Y. Reginald M. Atwater, M.D., is Executive Secretary.

OBITUARIES

DR. ARTHUR MONTELL SMITH

On July 21, 1944, Dr. Arthur Montell Smith, F.A.C.P., died at the Merritt Hospital in Oakland, California. Dr. Smith was born in Topshan, Maine, on March 18, 1872.

Before the age of 20 he came to California with his family, settling in San Jose, California. He began his medical studies with Dr. Bangs in San Jose and later entered the Cooper Medical College in San Francisco, receiving his M.D. degree in 1899. Shortly after graduation he began the practice of medicine at Merced, California, where he practiced for about five years. His next move was to Oakland, California where he began practice first as a general practitioner, later doing postgraduate work in eastern medical centers and preparing himself for the specialty of internal medicine. He served as a Captain in the Medical Corps during World War I and was stationed at Camp Kearny, later serving overseas. He served as Chief of the Medical Staff of the Samuel Merritt Hospital in Oakland for over 30 years. He was also at one time Superintendent of the Alameda County Hospital, and during his early carcer he was Health Officer for the City of Oakland. At one time he was on the California State Board of Medical Examiners.

His medical society memberships included the Alameda County Medical Society, California State Medical Society, and California Academy of Medicine. He was a Fellow of the American Medical Association and also a Fellow of the American College of Physicians since 1922.

Dr. Smith had retired from active practice in 1943. He leaves a widow, Mrs. Laura Luers Smith, and a daughter, Marian, who is the wife of Major Paul Sampson of the Army Medical Corps.

ERNEST H. FALCONER, M.D., F.A.C.P.,
Governor for Northern California

DR. LINDSAY STEPHEN MILNE

Dr. Lindsay Stephen Milne, F.A.C.P., of Kansas City, Mo., passed away at his home on September 17, 1944, following an illness of several months.

Dr. Milne was born in Montrose, Scotland, May 8, 1883. He graduated from the Montrose Academy in 1899, and obtained his Medical Degree at the University of Edinburgh, Scotland, in 1904. He was a Fellow of the Royal College of Physicians of Scotland. For a time, he was Instructor in the Departments of Pathology and Internal Medicine at his Alma Mater.

Dr. Milne was engaged in research work for a considerable period of time in Panama, Costa Rica, Brazil and South Africa. In 1908, he became affiliated with the Russell Sage Foundation and later with the Rockefeller

Institute for Medical Research, and was engaged in research in Pathology, chiefly on the liver. In 1912, he went to Kansas City, Mo., to head the Department of Medicine and to become Professor of Internal Medicine at the University of Kansas School of Medicine. He served as a Captain in the Medical Corps of the Army during World War I, having been stationed at Camp Funston, Kan., on the Mexican Border, Camp McPherson, Ga., and with the A.E.F. in France, where he was the Commanding Officer of Base Hospital No. 28, the Kansas City Unit. He was advanced to the rank of Colonel.

Dr. Milne practiced medicine in Kansas City until July, 1944, and had served in recent years as Attending Physician to the Kansas City General, Research and St. Luke's Hospitals. He was a Diplomate of the American Board of Internal Medicine and was the author of several published papers.

A fellow townsman has written: "In his thirty years residence in Kansas City, Dr. Lindsay Stephen Milne had established himself as an important factor in the city's medical life. To a rare degree, he combined thorough medical training, fine judgment and rare human sympathy. His death removes from this community not only a distinguished man of medicine, but a great human being."

DR. HARRY ALLEN RICHTER

Dr. Harry Allen Richter, F.A.C.P., Chicago, died July 8, 1944, of carcinoma; aged, 47. Dr. Richter was born in Chicago on August 27, 1896. He graduated from Northwestern University Medical School in 1923, and later did postgraduate work at the Massachusetts General Hospital, Boston. He was Associate in Medicine at Loyola University School of Medicine; Cardiologist at the St. Francis and Swedish Covenant Hospitals; and Associate Staff Physician, Cook County Hospital.

Dr. Richter was the former historian of the Chicago Medical Society; he was a member of the Illinois Medical Society, American Heart Association and American Therapeutic Society; a Fellow of the American Medical Association, and a Fellow of the American College of Physicians since 1940. He had published a number of medical articles.

DR. EDWARD SHEARMAN McSWEENY

Dr. Edward Shearman McSweeny died of coronary thrombosis on September 17, 1944. Dr. McSweeny was one of the charter Fellows in The American College of Physicians and led a long and active medical life in New York City.

He was born in 1877; attended St. Francis Xavier College; M.D., 1897, and D.P.H., 1921, Bellevue Hospital Medical College; postgraduate work, 1900–01, University of Berlin, University of Munich and private courses in Vienna. In his early career he was partially interested in surgery, and was

for the period 1901–05, Surgeon, O.P.D., St. Vincent's Hospital, New York City; at the same time, however, he was Demonstrator in Anatomy at New York University Medical School and Physician to the Foundling Hospital. He was at one time President of the Medical Board, St. John's Hospital, and Consultant to the Loomis Sanatorium and Grasslands Hospital, and member of the Medical Board of the Stony Wold Sanatorium; also member of the Medical Board at Gabriel's Sanatorium and the Workmen's Circle Sanatorium (Liberty). He later became Director of the Tuberculosis Preventorium and Trustee of the Potts Memorial Hospital; he had been also Medical Superintendent of the Sea View Hospital in Castleton Corners, N. Y., and the Tuberculosis Sanatorium of the New York City Department of Health in Otisville, N. Y.; he was also Medical Director of the New York Telephone Company and Consulting Physician to the Mary Immaculate Hospital, Jamaica, and St. John's Long Island City Hospital, Long Island City.

He was a former President of the New York Celtic Medical Society and of the Bellevue Alumni Society; former Secretary-Treasurer of the American Sanatorium Association; member of the New York County and State Medical Societies, New York Academy of Medicine, Harvey Medical Society, New York State Society of Industrial Physicians, New York Tuberculosis Association, National Tuberculosis Association, American Association for Thoracic Surgery, American Trudeau Society; Fellow, American Medical Association; Fellow of the American College of Physicians (charter member), June 25, 1915; Diplomate, American Board of Internal Medicine; died September 17, 1944, of coronary thrombosis; aged 66.

Dr. McSweeny was very actively interested in medical matters up until the time of his death.

Asa L. Lincoln, M.D., F.A.C.P.,
Governor for Eastern New York

DR. EDWARD C. GAGER

Dr. Edward C. Gager, F.A.C.P., was born in Saint Paul, December 16, 1882. He graduated from Central High School in 1900 and received his M.D. degree from the University of Minnesota Medical School in 1905.

He began practicing in Chamberlain, South Dakota, and later moved to North Branch, Minnesota. He began practice in Saint Paul in 1908 and became interested in dermatology, taking postgraduate work in Paris, Vienna, and the Postgraduate Medical Hospital in New York. Then for several years he was Assistant Professor of Dermatology of the University of Minnesota Medical School, and later Chief of the Venereal Disease Clinic of the Wilder Dispensary as well as Attending Dermatologist of Ancker Hospital.

Dr. Gager was a member of the Ramsey County Medical Society, the Minnesota State and American Medical Associations, the American College of Physicians, the Minnesota Dermatological Society, and The American Medical Association.

He died July 29, 1944, at the age of sixty-two of acute myocardial failure following an operation for intestinal obstruction due to gallstones in the ileum. He is survived by three brothers, Paul C. of Memphis, Tennessee, Alfred R. of State College, Pennsylvania, and Ray R. of Saint Paul.

REAR ADMIRAL CHARLES ST. JOHN BUTLER

Medical Corps, USN, Retired

In the death of Rear Admiral Charles St. John Butler, F.A.C.P., on October 7, 1944, at his home in Bristol, Tennessee the Medical Corps of the Navy lost one of its most eminent members and the American College of Physicians, one of its most distinguished Fellows. Admiral Butler was no ordinary individual but one who at all times at once arrested the attention. Large and massive in stature, his intellect was on a proportionate scale with his physical appearance. His strongly marked and emphatic personality made him what journalists are fond of referring to as a "Stormy Petrel." It must not be supposed, however, from this description that there was anything forbidding or ungracious about him. On the contrary, he was kindness itself and a most engaging and considerate physician and administrator, but a love of truth and unflinching integrity so ruled him that he was most outspoken in the defense of any scientific fact, or of any measure to better conditions which he felt were not right. He had the true zeal of a reformer and it was this characteristic which played a part in his great success as a medical administrator.

In the Virgin Islands, he was Commanding Officer of the Naval Hospital and Health Administrator of the islands and as head of the Public Health Service in Haiti, he was outstandingly successful. An eminent authority on tropical medicine has declared that Admiral Butler's work in the Virgin Islands in eliminating tropical disease was, on a small scale, as remarkable as that done by General Gorgas in Panama. In Haiti Admiral Butler is regarded as the man who did the most in the conquest of tropical disease in that island.

Admiral Butler will be remembered as connected with two interesting problems of tropical medicine and medical history. One was the unity of yaws and syphilis and the other, the controversy as to the Old World origin of syphilis as against the origin in the Americas. He was a strong believer in the unity of syphilis and yaws and a strong advocate of the theory that syphilis had existed in Europe prior to the Columbian voyages. On both of these subjects, Admiral Butler wrote and lectured extensively and his pronounced and vigorous views have some of the force and character of the

old Renaissance scientists. He was a learned and ingenious controversialist and his sound scholarship made his views and arguments difficult to overthrow.

He was a notable teacher of tropical medicine. The Medical Corps of our Navy and the Medical Corps of the Army were pioneers in tropical medicine in the United States, and the Naval Medical School for the first two decades of the present century was a principal center for the teaching of this specialty in this country. In the present war the success or failure of naval or amphibious operations in the tropics has depended many times on the knowledge of tropical diseases and the methods of their prevention. The training given our medical officers by men like Admiral Butler did much to enable them to cope successfully with these threats and protect our fighting forces from enemies more deadly even than armed men. Admiral Butler himself, must have realized this and have taken pleasure in the thought that he had so helped the Medical Corps of the Navy in the world's greatest war even though age had placed him in retirement.

Admiral Butler was born in Bristol, Tennessee, March 1, 1875, educated at Kings College, Emory and Henry College at Emory, Virginia and graduated in medicine from the University of Virginia in 1897. He was commissioned Assistant Surgeon in the Navy November 8, 1900. His first duty was on the old United States Fisheries Commission steamer *Albatross,* on which he served as Medical Officer and where his strong bent for scientific investigation was also utilized. Throughout his career, he served in many parts of the world and held many important positions. He was an instructor in bacteriology and tropical medicine at the U. S. Naval Medical School; Commanding Officer of the Naval Medical School and at one time acted as Professor of Medicine in the George Washington University School of Medicine. In addition to the posts which have been previously mentioned in the Virgin Islands and in Haiti, he had been Commanding Officer of the Naval Medical Supply Depot, Brooklyn, N. Y., the Naval Medical Center in Washington, D. C., and President of the Board of Medical Examiners for Officers of the Medical Corps. He served on the National Research Council and he was a member of many scientific and professional societies, including the Association of Military Surgeons, the American Academy of Tropical Medicine, American Society of Tropical Medicine and the Society of American Bacteriologists. He was the author of many professional papers and of a book, "Syphilis Sive Morbus Humanus," dealing particularly with the history of syphilis and yaws.

His death is a distinct loss in the fields of tropical medicine and medical history and to his many friends throughout the world.

Ross T. McIntire, F.A.C.P.,
Vice Admiral, (MC),
A.C.P. Governor for the U. S. Navy

DR. EDWARD MELVIN GREEN

Dr. Edward Melvin Green, M.D., F.A.C.P., of Harrisburg, Pennsylvania, former Superintendent of the Harrisburg State Hospital, died on September 30, 1944. Dr. Green was 77 years of age, was born in Washington, Goergia, July 10, 1867. He graduated from Centre College in 1887, receiving his Master of Arts degree from that institution in 1890, the same year in which he received his degree of Doctor of Medicine from the University of Pennsylvania School of Medicine. He did post-graduate work at the Jefferson Medical College Hospital in Philadelphia; Manhattan State Hospital in New York; and from 1891 to 1895 was assistant physician at the Eastern Kentucky State Hospital for the Insane. During 1896 and 1897 he was Physician in Charge of the Oklahoma State Hospital; from 1901 to 1917 he was on the Staff of the Milledgeville State Hospital, Georgia, and left a clinical directorship at that hospital in 1917 to become Superintendent of the Harrisburg State Hospital, which position he held until his retirement in 1934. Following his retirement he engaged in consultation practice, and was consultant at the Harrisburg Polyclinic and the Lancaster County Hospitals, and was Director of the Neuropsychiatric Service at the York (Pennsylvania) Hospital for several years. He was a Fellow of the American Psychiatric Association, the American College of Physicians and the American Medical Association. He was the author of numerous papers, several of which on psychoses in negroes attracted wide attention. In 1942, in spite of his advancing years, he returned to aid in the work of the Harrisburg State Hospital, and throughout the War period was an active member of the Medical Advisory Board of the Pennsylvania Selective Service. A physician of high ideals and gracious Christian character, possessed in a marked degree of the quality of dignity, imperturability and gentleness, he maintained the high standards of his profession, and was held in great respect in the community in which he lived, and where he was active in his support of worth while public projects. He is survived by his wife, Ann C. Green; and two sons—Lieutenant Edward M. Green, Jr., USNR; and Louis C. Green, Ph.D., on the teaching Staff at Bryn Mawr College. Interment was at Dr. Green's boyhood home, Danville, Kentucky.

H. K. Petry, M.D., F.A.C.P.

THE AMERICAN COLLEGE OF PHYSICIANS

MEMBERS OF THE BOARD OF GOVERNORS

Term Expiring 1945

Roy E. Thomas, Los Angeles	CALIFORNIA (Southern)
Ward Darley, Denver	COLORADO
Charles H. Turkington, Litchfield	CONNECTICUT
Wallace M. Yater, Washington	DISTRICT OF COLUMBIA
Cecil M. Jack, Decatur	ILLINOIS (Southern)
Robert M. Moore, Indianapolis	INDIANA
Harold H. Jones, Winfield	KANSAS
Chester S. Keefer, Boston	MASSACHUSETTS
Warren Thompson, Omaha	NEBRASKA
Nelson G. Russell, Sr., Buffalo	NEW YORK (Western)
Leander A. Riely, Oklahoma City	OKLAHOMA
*Thomas M. McMillan, Philadelphia	PENNSYLVANIA (Eastern)
R. R. Snowden, Pittsburgh	PENNSYLVANIA (Western)
John L. Calene, Aberdeen	SOUTH DAKOTA
William C. Chaney, Memphis	TENNESSEE
Louis E. Viko, Salt Lake City	UTAH
Harry L. Arnold, Honolulu	HAWAII
Warren S. Lyman, Ottawa	ONTARIO
Francisco de P. Miranda, Mexico City	MEXICO
Gilbert M. Stevenson, Ancon	REPUBLIC OF PANAMA and the CANAL ZONE

Term Expiring 1946

Oliver C. Melson, Little Rock	ARKANSAS
Ernest H. Falconer, San Francisco	CALIFORNIA (Northern)
Benjamin F. Wolverton, Cedar Rapids	IOWA
Edgar Hull, New Orleans	LOUISIANA
*Patrick L. Ledwidge, Detroit	MICHIGAN
*Edward H. Rynearson, Rochester	MINNESOTA
Ralph Kinsella, St. Louis	MISSOURI
Lawrence Parsons, Reno	NEVADA
Harry T. French, Hanover	NEW HAMPSHIRE
George H. Lathrope, Newark	NEW JERSEY
Paul F. Whitaker, Kinston	NORTH CAROLINA
Julius O. Arnson, Bismarck	NORTH DAKOTA
Alexander M. Burgess, Providence	RHODE ISLAND
Kenneth M. Lynch, Charleston	SOUTH CAROLINA
*Ellsworth L. Amidon, Burlington	VERMONT
J. Edwin Wood, Jr., University	VIRGINIA
*Edwin G. Bannick, Seattle	WASHINGTON
Walter E. Vest, Huntington	WEST VIRGINIA
Hugh A. Farris, St. John	MARITIME PROVINCES
Charles F. Moffatt, Montreal	QUEBEC

Term Expiring 1947

Fred W. Wilkerson, Montgomery	ALABAMA
Fred G. Holmes, Phoenix	ARIZONA
Lewis B. Flinn, Wilmington	DELAWARE
Turner Z. Cason, Jacksonville	FLORIDA
Glenville Giddings, Atlanta	GEORGIA
Samuel M. Poindexter, Boise	IDAHO
Walter L. Palmer, Chicago	ILLINOIS (Northern)
C. W. Dowden (*Chairman*), Louisville	KENTUCKY
*Richard S. Hawkes, Portland	MAINE
Wetherbee Fort, Baltimore	MARYLAND
John G. Archer, Greenville	MISSISSIPPI
Ernest D. Hitchcock, Great Falls	MONTANA
Robert O. Brown, Santa Fe	NEW MEXICO
Asa L. Lincoln, New York	NEW YORK (Eastern)
A. B. Brower, Dayton	OHIO
Homer P. Rush, Portland	OREGON
M. D. Levy, Houston	TEXAS
Elmer L. Sevringhaus, Madison	WISCONSIN
Ramon M. Suarez, San Juan	PUERTO RICO
John W. Scott, Edmonton	ALBERTA, BRITISH COLUMBIA, MANITOBA, SASKATCHEWAN

Ex Officio

Norman T. Kirk	United States Army
Ross T. McIntire	United States Navy
Thomas Parran	United States Public Health Service

* Acting Governor.

ANNALS OF INTERNAL MEDICINE

Official Periodical of the American College of Physicians

Place of Publication—Prince and Lemon Sts., Lancaster, Pa.

Editorial Office—University Hospital, Baltimore, Md.

Executive Office—4200 Pine Street, Philadelphia, Pa.

The Annals of Internal Medicine is published by the American College of Physicians. The contents consist of contributions in the field of internal medicine, editorials, book reviews, and a section devoted to the affairs of the College.

Manuscripts. All correspondence relating to the publication of papers and all books and monographs for review should be addressed to the editor. No manuscripts will be accepted without his consideration. Bibliographic references are to conform to the following style:

4. Doe, J. E.: What I know about it, Jr. Am. Med. Assoc., 1931, xcvi, 2006–2008.

Six illustrations per article are allowed without cost to the author. Beyond this number the author must pay the actual cost of illustrations.

Reprints. For each article published, there will be furnished gratis fifty reprints without covers. An order slip for additional reprints, with a table showing cost, will be sent with galley proof to each contributor. If additional reprints over the first fifty are wanted the order slip must be returned to the printer at the time corrected galley proofs are sent to the Editor.

Reviews. The Annals will make an especial feature of the reviews of monographs and books bearing upon the field of internal medicine. Authors and publishers wishing to submit such material should send it to the editor. While obviously impossible to make extended reviews of all material, an acknowledgment of all books and monographs sent will be made in the department of reviews.

Subscription. This periodical is issued monthly, new volumes beginning with the January and July numbers of each year. Subscriptions may be by the volume or year. Volumes will consist of approximately 1,000 pages. Subscription price per annum, net postpaid: $7.00, United States, Canada, Mexico, Cuba, Canal Zone, Hawaii, Puerto Rico; $8.00, other countries. Prices for back volumes or numbers furnished upon application. Single numbers, current volume, when available, $1.00. Members of the American College of Physicians receive the Annals of Internal Medicine in connection with the payment of annual membership dues, of which seven dollars is for a year's subscription to the publication. Checks should be drawn to the order of W. D. Stroud, M.D., Treasurer, and remitted through the Publication Office or the Executive Secretary's Office.

Business Correspondence. All correspondence relating to business matters, advertising, subscriptions to the Annals, inquiries concerning membership in the American College of Physicians, et cetera, should be addressed to the Publication Office or to the Executive Secretary. Books and reprints presented to the College Library should be addressed to the Executive Secretary.

Lancaster Press, Inc., Lancaster, Pa.

Index photographed at the
beginning for the convenience
of the microfilm user.